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P R O C E E D I N G S

Agenda Item: Opening Remarks

DR. MODLIN: My name is John Modlin, from Dartmouth Medical School. I'm the chair of VRBPAC. I would like to call this morning's meeting to order and welcome all our members, voting members and non-voting members, who are joining us and, of course, all of our guests as well.

I'm going to turn things over to Christine Walsh, who has a few administrative matters to update us on.

MS. WALSH: Thank you, Dr. Modlin, and good morning, everyone.

I'm Christine Walsh, the designated federal officer for today's meeting of the Vaccines and Related Biological Products Advisory Committee. I would like to welcome all of you to this meeting.

Today's session will consist of presentations that are open to the public. I would like to request that everyone to check their cell phones and pagers and make sure they are off or in the silent mode. I would also like to just let the committee know for those of you who were here yesterday, we had the microphones switched to push-to-talk so it will not automatically, so you do need to push to talk. Also if the committee could please not leave your cell phones or your Blackberrys next to the microphones because I believe that was causing some static also. Thank you.

I would now like to read into the public record the conflict-of-interest statement for today's meeting. This brief announcement is in addition to the conflict-of-interest statement read at the beginning of the meeting on February 18 and will be part of the public record for the Vaccines and Related Biological Products Advisory Committee meeting on February 19, 2009. This announcement addresses conflicts of interest for Topic 3, the discussion of the conducting of clinical studies of pandemic influenza vaccine in the pediatric population in the absence of an influenza pandemic. This is a particular matter involving specific parties.

Based on the agenda and all financial interests reported by members and consultants related to Topic 3, no conflict-of-interest waivers were issued under 18 USC 208(b)(3) and 712 of the Food, Drug, and Cosmetic Act. Dr. Seth Hetherington is serving as the industry representative, acting on behalf of all related industry, and is employed by Icagen, Incorporated. In addition, Dr. Hetherington's spouse is employed by GlaxoSmithKline. Industry representatives are not special government employees and do not vote.

With regard to FDA's guest speaker for Topic 3, the agency has determined that the information provided is essential. The following information is being made public to allow the audience to objectively evaluate any presentation and/or comments.

Dr. Bettie Voordouw is head clinical assessor for anti-infectives, Pharmacotherapeutic Group 1, Medicines Evaluation Board, The Hague, the Netherlands. Her spouse is employed by Pfizer in the Netherlands, but is not involved in the human vaccine shield.

In addition, there may be regulated industry and other outside organization speakers making presentations. These speakers may have financial interests associated with their employer and with regulated firms. The FDA asks that, in the interests of fairness, they address any current or previous financial involvement with any other firm whose product they may wish to comment upon. These individuals were not screened by the FDA for conflict of interest.

The conflict-of-interest statement will be available for review at the registration table.

We would like to remind members and participants that if the discussions involve any of the products or firms not already on the agenda for which an FDA participant has a personal or imputed financial interest, the participants need to exclude themselves from such involvement, and their exclusion will be noted for the record. FDA encourages all other participants to advise the committee of any financial relationships that you may have with any firm, its products, and, if known, its direct competitors.

Thank you.

Dr. Modlin?

DR. MODLIN: Thanks, Christine.

I would like to ask each of those who are seated at the table to briefly introduce themselves and their institutional affiliations. I think we will start on this side, beginning with Dr. Nelson.

DR. NELSON: Robert Nelson. I'm the pediatric ethicist with the Office of Pediatric Therapeutics at FDA.

DR. PRATT: Douglas Pratt. I'm chief of the Clinical Trials Branch in the Division of Vaccine Applications, Office of Vaccines, FDA.

DR. BAYLOR: Norman Baylor, director of the Office of Vaccines Research and Review at CBER, FDA.

DR. WHARTON: Melinda Wharton, acting director, Immunization Safety Office at the Centers for Disease Control.

DR. DESTEFANO: Frank DeStefano, senior research epidemiologist, RTI International.

DR. STAPLETON: Jack Stapleton, director of the Division of Infectious Diseases, University of Iowa.

DR. LEVANDOWSKI: Roland Levandowski. I'm an infectious-diseases physician. I have no institutional associations.

DR. GELLIN: Bruce Gellin, director of the National Vaccine Program Office at HHS.

DR. JOFFE: Steve Joffe, a pediatric oncologist at the Dana-Farber Cancer Institute and Children's Hospital in Boston. I'm the Dana-Farber hospital ethicist.

DR. FOST: Norm Fost, professor of pediatrics and director of the Bioethics Program at the University of Wisconsin.

DR. HETHERINGTON: Seth Hetherington, senior vice president for clinical and regulatory affairs, Icagen, Incorporated, in Research Triangle Park, North Carolina.

DR. ROMERO: José Romero. I'm the section chief of pediatric infectious diseases and professor of pediatrics at the University of Arkansas for Medical Sciences, as well as the director of their clinical research program.

DR. MCINNES: Pamela McInnes, National Institutes of Health.

DR. GILBERT: Peter Gilbert, Vaccine and Infectious Disease Institute, Fred Hutchinson Cancer Research Center in Seattle.

DR. SANCHEZ: Pablo Sanchez, a neonatologist and pediatric ID at UT Southwestern, Dallas.

DR. EICKHOFF: Ted Eickhoff, University of Colorado, Denver, infectious disease.

DR. KLIMOV: Alexander Sasha Klimov, Influenza Division, Centers for Disease Control and Prevention, Atlanta.

DR. JACKSON: Lisa Jackson. I'm a vaccine researcher at the Group Health Center for Health Studies in Seattle.

DR. DAUM: I'm Robert Daum. I'm a professor of pediatrics at the University of Chicago, infectious diseases, a past member of the Pediatric Advisory Committee of the FDA, and a past chair of this committee.

DR. MODLIN: Thanks, Bob. I understand that Dr. Debold is stuck somewhere underground on the metro -- can of like Charlie on the MTA -- and will be joining us as soon as she can.

This morning the Vaccines and Related Biological Products Advisory Committee is meeting. We are joined by a few members of the Pediatric Advisory Committee, I understand. As Christine said, the focus of our discussion throughout the entire day will be the conduct of clinical studies involving children with regard to pandemic influenza candidate vaccines.

Dr. Pratt, I understand that you are going to lead with some introductory comments.

**Agenda Item: Topic 3: Clinical Studies with
Pandemic Influenza Candidate Vaccines in the Pediatric
Population in the Absence of an Influenza Pandemic**

Introduction

DR. PRATT: Good morning.

As mentioned, the topic today is clinical evaluation of pandemic influenza vaccines in children.

This is an agenda for the day's activities. I will be introducing the topic and provide some background for the discussion. Bettie Voordouw, who is a member of the Vaccines Working Party at EMEA, will follow with the European perspective on these issues. Skip Nelson will walk us through the Subpart D regulations, the additional safeguards for children in clinical studies.

There will be three sponsor presentations that will follow: from GlaxoSmithKline, by David Vaughn; from Novartis, by Theodore Tsai; and from NIAID, by Richard Gorman.

Then I'll return later in the day to present some discussion points for the committee to consider.

My presentation this morning:

- Will summarize the relevant epidemiology for H5N1 in relation to children. I'll go over the definitions of pandemic vaccine and pre-pandemic vaccines, as FDA has defined them.

- I'll go over the Pediatric Research Equity Act.

- I'll introduce the Subpart D regulations, though Skip Nelson will go into those in far more detail.

- I'll go over age considerations for pandemic vaccines, touching on the allocation priority from the departmental guidance, as well as the seasonal influenza recommendations as they relate to age and children.

- I'll summarize the ongoing and completed H5N1 vaccine studies in children to date.

- I'll touch on some safety considerations.
- Go over existing FDA guidance.
- If time permits, I'll preview the discussion points for the committee.

The WHO has been tracking cases of H5N1 since 2003. There have been 404 human cases of H5N1. That's updated as of February 2 of this year. Sixty-three percent of these cases have been fatal.

Most cases have been among people in contact with domestic poultry. All human cases have been in either Asia or Africa. No avian or human cases of highly pathogenic H5N1 have yet been reported in the Western Hemisphere.

These data are somewhat dated. They are from June of 2006. These were the last published data from WHO, breaking down the cases by age. One can see that most of the cases of H5N1 have been in children and in young adults, and relatively fewer cases among the older age groups.

With respect to severity of disease, the highest mortality is actually in the adolescent age group, 10- to 19-year-olds. You can focus here on the first column and the last column. The last column has the cumulative data. The 10- to 19-year-olds have a 73 percent case fatality rate for H5N1; also still high in the young adults; somewhat lower in the younger children and older adults, but still quite high.

At this point I would like to try to distinguish the indications for a pandemic vaccine versus a pre-

pandemic vaccine. A pandemic vaccine, as FDA is using the term, is for active immunization of persons who are at increased risk of exposure to an influenza virus that has potential to cause an influenza pandemic, and then during a pandemic caused by the influenza virus subtype contained in the vaccine. We envision that these vaccines would be used under an emergency declared by the secretary.

By contrast, a pre-pandemic vaccine indication would be for active immunization of persons against an influenza virus subtype that has the potential to cause a pandemic, as a strategy for pandemic preparedness. The distinction here would be that this would be for use during the interpandemic period, before a pandemic is declared, for example, for population priming and boosting.

This distinction is important when considering vaccine development and the kinds of data one might expect for either indication. In a true pandemic, in an emergency setting, it's likely that any safety risks from the vaccine would be far outweighed by potential anticipated benefits from the vaccine. In a pre-pandemic setting, when one cannot know for certain the subtype or the strain of the future pandemic, the anticipated benefits are less certain, and one might expect more safety data to support the routine use in that situation.

Specific laws and regulations apply to clinical research conducted in children. The Pediatric Research Equity Act -- we refer to it as PREA -- was enacted in

2003. It was renewed in 2007 with the FDA Amendments Act. The intent of this legislation was to assure that children have access to safe and effective drugs, through proper testing for pediatric use. The regulation calls for a pediatric assessment for all relevant pediatric populations -- this is required -- and all applications or supplements for new active ingredients, new indications, dosage forms, dosing regimens, or routes of administration.

The pediatric assessment should contain data from pediatric studies for each age group for which the assessment is required. These data should be adequate to assess the safety and effectiveness for claimed indications in all relevant pediatric subpopulations and should be adequate to assess the dosing and administration.

FDA reviews these assessments. In fact, we have an internal FDA-wide advisory committee that participates in the review process. This is the PER (phonetic) committee. After review, based on provisions in the law, FDA may conclude that the assessment is adequate to support the safety and effectiveness in all age groups or -- item 2 here -- the findings in the assessment can be extrapolated from adults to children or between age groups, if the course of the disease and the effects of the vaccine are sufficiently similar.

Also FDA could, alternatively, defer studies, in which case they would be provided at a later agreed-upon date.

Finally, it's also possible that studies would be waived and never requested. There are specific conditions in which this would occur. For instance, if the necessary studies were impossible or impracticable to conduct or if there is evidence that the product would be unsafe or ineffective in children.

What have we done so far with respect to PREA? We have licensed one pandemic vaccine. This is the Sanofi Pasteur influenza virus vaccine H5N1, for the National Stockpile. The indication for that vaccine reads, "For active immunization of persons 18 through 64 years of age at increased risk of exposure to the H5N1 influenza virus subtype contained in the vaccine." Of note here is that the indication is for adults; it is not for children.

Also of note here is the dosage and administration. The antigen is at a higher concentration than is in seasonal vaccines, and two doses are required, even for adults.

With respect to PREA, the pediatric studies required under PREA for this vaccine were deferred. The deferred status is to be reassessed upon review of data from a completed pediatric study. At the time that we met for the advisory committee to discuss this vaccine, this trial was mentioned briefly. The manufacturer has committed to submit these data to assess the safety and reactogenicity of the vaccine. The protocol is entitled "A Randomized, Double-Blind Phase I/II Study of the Safety,

Reactogenicity, and Immunogenicity of H5N1 Vaccine in Healthy Children Aged 2 Years through 9 Years of Age." I ask you to make note of the age there because we will come to age considerations.

At this point, I would like to introduce the Subpart D regulations. Of course, children cannot provide informed legal consent, and a set of federal regulations were adopted to assure that research conducted in children preserves their rights and safety. These additional safeguards in Subpart D have applied to federally funded research since 1983, under the 45 CFR regulations. In 2001, the FDA regulations under 21 CFR were updated to incorporate these safeguards. These now apply to all FDA-regulated research, including research sponsored by manufacturers.

Again, I'll just introduce these briefly. Skip Nelson will go over them in some detail.

Under Subpart D, research in children can be approved by an IRB, under four sets of conditions:

- 50.51 states that if the research does not involve more than minimal risk, the studies can go forward.
- 50.52 states that if the research presents the prospect of direct benefit for the individual subject, the research can be approved.
- Under 50.53, if the risk represents a minor increase over minimal risk and the research is likely to

yield generalizable knowledge about the subject's disorder or condition, the research could be approved.

I'll stop here and say that in the FDA briefing document, a somewhat restricted interpretation of "disorder or condition" was taken, in that a healthy child would not have a disorder or condition and this might not apply. I think Dr. Skip Nelson will go over this in more detail, and perhaps a broader interpretation may apply here.

If clinical investigations involving children are not approvable under the three regulations that I have just cited, the research can still go forward if it presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health and welfare of children. However, an IRB cannot approve that research. Under this provision, the trial must be referred to the FDA Commissioner for a panel review. The Pediatric Advisory Committee serves as the reviewing panel for FDA if these studies are referred under 50.54.

Once previously, a vaccine trial was referred under 50.54. I know a couple of members of the advisory committee have familiarity with this example. In 2002, a clinical trial of a live vaccinia smallpox vaccine in children 2 to 5 years of age was referred by an IRB. This trial was sponsored by NIAID. In fact, two IRBs approved the trial. One IRB referred the trial for panel review under Subpart D. They cited a lack of the prospect of

direct benefit and also that determining risk in this situation was very difficult.

A panel of 10 experts was organized by the Office of Human Research Protections, and they provided written opinions regarding the approvability of the study. This was not a meeting in one place at one time. But these opinions are published and they are available publicly.

The panel did find that the research was approvable, and most agreed that it was approvable under the 50.54 regulation -- that is, that it provided the opportunity to understand, prevent, or alleviate a serious problem affecting the health and welfare of children.

Ultimately, this study was not conducted, because another means of addressing the availability of smallpox vaccine was pursued by the Department.

At this point, I would like to move on to age considerations. This figure is from the guidance from the Department on allocation of pandemic influenza vaccines in the event of a pandemic. It may be a little difficult to read from the back of the room.

In tier 1, which is the highest priority in a severe pandemic, that group includes pregnant women, infants, and toddlers; in tier 2, high-risk children -- that is, children with medical conditions that would place them at high risk -- as well as infant contacts. Then healthy children aged 3 to 18 are actually in tier 3 in this plan.

This slide summarizes the data from the earlier figure. Again, in tier 1 are pregnant women, infants, and toddlers, 6 months through 35 months of age. The plan determined that children under 6 months of age would not be a priority because there are no seasonal vaccines that are licensed in that age group, and there was thinking that there vaccines would not work in that age group. The way of addressing that was that household contacts of infants less than 6 months of age were considered high-priority in tier 2. Again, tier 3 is children 3 to 18 years of age who are without high-risk medical conditions.

So that's one way of thinking about age of children in the event of a pandemic.

Also relevant to age of children as we discuss this issue are the seasonal recommendations for influenza vaccines. These are current from 2009, from the ACIP. The seasonal influenza recommendations say that the minimum age is at 6 months of age for the trivalent inactivated influenza vaccine and 2 years of age for the live, attenuated vaccine. All children should be vaccinated yearly from age 6 months through 18 years, and children receiving TIV should get .25 mL if they are aged 6 to 35 months and then .5 mL if they are aged 3 years or older. So there is an age break here. Children less than 9 years of age should receive two doses if they are receiving influenza vaccine for the first time or if they were vaccinated for the first time in the previous

influenza season, but only received one dose. So again, we have two age breaks here at 3 years and 9 years of age.

Some clinical trials have already been initiated and some completed in H5 influenza vaccines in children. These trials were identified from a search of the Clinicaltrials.gov database. They are not all necessarily being conducted under a U.S. IND. Some of the information is supplemented from other public sources.

What I ask you to note here are the different ages that the different manufacturers are studying, again the different locations, and the sizes of these trials.

With the first trial noted here, the Sanofi trial in 2- to 9-year-olds, that is the trial that was mentioned earlier and was mentioned at the previous VRBPAC.

All of these trials so far are using the A/Vietnam/2004 subtype vaccine. Also of note is that some of these contain different adjuvants, either aluminum phosphate or aluminum hydroxide adjuvants, or in the case of GSK, their AS03 adjuvant, and in the case of Novartis, their MF59 adjuvant.

Important to the discussion of risk in the context of the Subpart D regulations is the safety of the vaccines. I have listed here some safety considerations. These actually apply for adults, as well as children, but in the context of pediatric trials, we do note that a larger antigen dose may be required than is

used for the seasonal vaccine. Certainly that was the case for the Sanofi vaccine that is approved.

They also may contain a novel adjuvant -- for example, the MF59 or the ASO3 that was just mentioned. I'll note here that these so-called novel adjuvants are not components of any U.S.-licensed vaccine yet, though they may be in some vaccines approved in Europe. In the U.S., certainly we have no long-term extensive record of safe use that we would get in a large pre-licensure study or from a postmarketing experience.

There are theoretical concerns with respect to these adjuvants of possible nonspecific self-directed immune responses that might be stimulated. Acknowledging that theoretical concern, no serious safety issue has been identified, I think we could say, based on the published data. Of course, we have not reviewed these in the context of an application.

With respect to the live influenza vaccines, the live pandemic vaccines would pose risks associated with replication, shedding, transmission, and possibly reassortants.

In 2007, FDA did put out a guidance for industry on the clinical data needed to support the licensure of pandemic influenza vaccines. With respect to the pediatric indications, the discussion is quite brief, and I'll read it here in the next couple of slides:

"It is anticipated that data will be collected in adults and in the pediatric population in a stepwise fashion. We assume that approval for use in the adult population, including the geriatric population, will be sought with the initial application. The amount of data needed for a particular sponsor's pandemic influenza vaccine to support approval for use in the pediatric population will depend on the available clinical data for that sponsor's U.S.-licensed seasonal influenza vaccine. The timing of the clinical development in the pediatric population warrants discussion with CBER."

So that's the extent of the guidance on pediatric trials that we published in 2007. I'll note, coming back to this slide, that clinical data from the sponsor's U.S.-licensed seasonal vaccine -- that is somewhat problematic when the vaccines contain these novel adjuvants.

At this point, I'll summarize the discussion:

- Children at all ages are at risk for pandemic influenza, and we note that avian influenza has infected and killed children in Asia and Africa.
- The timing, subtype, and clade/strain of the next influenza pandemic are not known. In fact, it may not be an H5N1 subtype.
- PREA, the Pediatric Research Equity Act, promotes the proper testing to assure that products are safe and effective for pediatric use. However, extrapolation of data from adults and across age groups can

address PREA requirements if the disease and effects of the vaccine are similar.

- Subpart D provides an ethical framework for conducting the clinical investigations in children.

- With respect to age, we have the seasonal influenza vaccine recommended dose and schedule, and we note that they do depend on the age of the child.

- We have the departmental guidance on allocation of pandemic vaccine during a severe pandemic and note that infants and toddlers are in tier 1 and children without other medical conditions are listed in tier 3.

- We also note that multiple manufacturers are investigating H5N1 vaccines in children, and the age groups being evaluated in the trials to date do vary among the manufacturers and the locations where these studies are conducted.

- Finally, novel adjuvants used in some pandemic vaccine candidates lack extensive safety experience in children.

- FDA guidance regarding pandemic influenza vaccine development for children does not address vaccines without a corresponding licensed seasonal vaccine or the specific age groups to be studied. They also do not address live, attenuated vaccines and the issues that might be relevant there.

So I'll stop at this point. If time permits, I could preview the questions. Up to the Chair.

DR. MODLIN: Actually, I think that would be a very good idea. Why don't we go ahead and take a look at the questions the committee will need to discuss?

DR. PRATT: There are two discussion items, with some sub-discussion points.

Discussion point 1: Please discuss whether clinical studies in one or more pediatric age groups should be conducted using inactivated pandemic influenza vaccine candidates as part of pandemic preparedness.

If your recommendation is that no clinical studies in any pediatric age group should be conducted prior to use of an inactivated pandemic influenza vaccine in children, please discuss whether other data, if any, would be needed to support immunizing children in the event of an influenza pandemic.

Item 1, continuing: If your recommendation is that clinical studies should be conducted in one or more pediatric age groups prior to use of an inactivated pandemic influenza vaccine in children, please discuss your recommendations regarding which pediatric subpopulations should be studied and also the adult safety and immunogenicity that would be needed to support proceeding to pediatric studies with inactivated pandemic influenza vaccine candidates. In your deliberations, please consider the use of novel adjuvants and additional viral subtypes, other than H5N1.

The last discussion point: Please discuss what pediatric safety and immunogenicity data you would consider adequate to support licensure of an inactivated pandemic influenza vaccine candidate for use in one or more pediatric populations. In your deliberations, please consider use of novel adjuvants and other viral subtypes, in addition to H5N1.

DR. MODLIN: Thank you, Dr. Pratt, for very clearly laying out the issues that we will be discussing today.

In the interest of time, I think we'll move on to the next item, which will be the European regulatory perspective by Dr. Bettie Voordouw.

Agenda Item: EMEA Perspective

DR. VOORDOUW: Thank you very much for giving me the opportunity to say something about the European perspective here in this audience.

This is very new for me and, I think, for many Europeans, because we don't have a setting like this. So it's very interesting to be here.

First of all, I would like to say that also in Europe the discussion with regard to pre-pandemic influenza vaccines in pediatric populations is not at all a closed discussion. We are still in the middle of it. What I'll be presenting now are the results of ongoing discussions over the last six to seven years.

What I would like to talk about is, first of all, very shortly, to say something about the European regulatory environment and then say something about seasonal influenza vaccines and how we apply those requirements for pre-pandemic influenza vaccines. I would like to stress in both cases what that might mean for pediatric populations and what it doesn't mean for pediatric populations. Finally, I would like to say what we really don't know.

The pictures on the right have nothing to do with the presentation, but give you some flavor of the Netherlands, where I come from.

First of all, the European regulatory environment: The EMEA is the European counterpart of the FDA. I think all of you know the EMEA. The main difference between EMEA and FDA is that it's an administrative body that is responsible for all EU-wide regulatory activities. But in addition to that, as you can see there, we have also 27 national authorities, national competent authorities, because we are 27 EU member states. So next to European legislation and regulations, we also have national regulations. It is sometimes very difficult to combine the two.

Moreover, the EMEA uses the expertise from the individual member states. For example, for the committees that you see there below, like the Committee for Human Medicinal Products, CHMP, the body that is responsible for

licensing human medicinal products, that expertise comes from all the different member states. But, for example, for the working parties, like the Vaccine Working Party, which I am a member of, that uses only specific expertise from some member states. In the Vaccine Working Party, we are from, I think, 10 or 12 different countries, and not 27.

So this is how the EMEA is constructed.

As I said, discussions concerning pediatric data in pandemic or pre-pandemic influenza vaccines are ongoing since we started talking about these vaccines. That was, I think, in 2002-2003. It was not until the EU Pediatric Regulation became active in 2007 that we got the tools in hand to bring the discussion much more actively forward.

The EU Pediatric Regulation led to the installation of the Pediatric Committee at the EMEA in 2007. The objectives of this committee are to:

- Improve the health of children through the increase of high-quality, ethical research into medicines for children.
- Increase availability of authorized medicinal products for children.
- Increase information on medicines.

To achieve the above, it has to be done without unnecessary studies in children and without unnecessarily delaying authorization for adults.

It has a strong similarity with the Equity Act in the U.S. I think that much of it has been -- we looked very carefully to the U.S. situation.

This was the setting, seasonal influenza vaccines. In the EU, as in other countries, of course, we have an annual relicensure procedure for seasonal influenza vaccines. But in the EU, contrary to other regions of the world, we request a seasonal immunogenicity trial for every vaccine that's licensed. That means that every manufacturer has to do a clinical study, an immunogenicity study, in 50 healthy adults and 50 healthy adult elderly, to support the new formulation. These are assessed based on the so-called CHMP criteria. They are defined according to the GMT increase, the seroconversion or a significant increase proportions, and the seroprotection rate.

It's important to note that there are no validated criteria for children. These studies are also done only in healthy individuals over 18. We have no validated criteria for children at all.

The question, of course, is, what CHMP criteria are relevant for pandemic or pre-pandemic vaccines. Of course, when you look at seasonal vaccines and pre-pandemic vaccines, there is a difference in pre-vaccination antibody titers. We assume that most of the population is immunologically naïve to a pandemic strain. There is a difference in vaccination or infection history. There is a difference in the use of adjuvants. Almost all pandemic

and pre-pandemic vaccines are using adjuvants, and it will influence the primary response. Very important, there is no license for adjuvants in influenza vaccines in children.

I must say here that in Europe all the seasonal influenza vaccines have licenses for use in children. So it's different from here. But none of them has a license for adjuvanted vaccines, and none of them has any experience in children.

The choice of dose for pandemic influenza vaccine is targeted at availability instead of on the efficacy. There is a difference, of course, in the schedule with regard to priming versus revaccination and, again, experience in children.

Is it acceptable to extrapolate data to children? It's evident from everything we have heard before that data in children are needed. Yesterday it became apparent; it was very clear from the discussions there that data in children are needed and appropriate influenza vaccines for children are needed. But it's very difficult to make the assumption that you can extrapolate seasonal data or pre-pandemic data to the use in children, because children are not young adults. They are immunologically more naïve, but maybe not for the pandemic strains. In theory, from our perspective, they might be the best model for serological assessment of pandemic strains, if you would reconsider your thoughts.

Furthermore, we know the seroconversion rates in children increase with age, with less than 50 percent seroconversion in children below 6 months of age, and more than 80 percent will seroconvert after influenza vaccination over the age of 10 years. That's probably also the influence of natural priming.

It led for us to the idea at least that data from younger adults were probably most representative only for those likely to be naturally primed. In essence, that means that you might accept an extrapolation to older pediatric populations, maybe children over 9 years, but not in children younger than 9 years or younger than 6 years.

As I said, it's inevitable that data on children are needed:

- As we have heard several times now, there is a difference in disease burden.
- There are differences in clinical characteristics of the disease.
- There is a difference in predictive benefit or assumed benefit.
- It's likely that immunological response will be different in children.
- We do not have any dose-response data for influenza vaccines in children, also with the seasonal vaccines.
- We have no long-term safety data in children, also for the seasonal vaccines.

- We also don't have them on the adjuvanted influenza vaccines.

- The question is, of course, are the seasonal criteria relevant for use in children? As I said before, they are not specific for children and they are not validated for use in children.

First of all, with all these limitations for use in children, how did we proceed for the pre-pandemic and pandemic influenza vaccines?

In Europe, different from here, we do have at some point to decide on the acceptability of a pre-pandemic or a pandemic vaccine and say whether it can be licensed, yes or no. When the manufacturer comes to us with a dossier, we have at some point to say whether it can be licensed, yes or no. We can't keep it in an IND.

Because of that, we installed two procedures, one for the pandemic vaccines and one for the pre-pandemic vaccines. For the pandemic, that's called a mock-up dossier. It's a dormant dossier and it means that the vaccine cannot be marketed in the pre-pandemic period. The indication will be based on official guidelines and the product can only be marketed after inclusion of the final pandemic strain.

For pre-pandemic vaccines, the situation is different. That is a full application. It means that the company is allowed to market the vaccine, but that will be up to the individual member states. One of my colleagues

had a comment here and said that, depending on the decision of the member states -- for example, France has decided not to market a pre-pandemic vaccine, whereas Finland has decided to prime the whole population. So there are regional differences in Europe regarding that.

The other difference is that, because it's marketed, it's a full application, so the dossier and the requirements are different. The indication will be restricted to the age groups that are studied. So if there are no pediatric data, there will be no pediatric indication. That's different from a pandemic strain, because the national governments may decide to vaccinate the whole population.

The interesting thing is that in practice these vaccines are the same; only the procedures are different. So we have identical vaccines licensed with a pandemic and a pre-pandemic license.

Of importance also for the pre-pandemic vaccine is that they have to maintain their dossier with drifted strains. We get regular updates if things change.

To make our lives easier, we have developed a lot of guidelines. I won't go into detail there. If anyone is interested, please go to the EMEA Web site and you can find them all, or on PDFs, if it's easier for you.

What do those guidelines, the two most relevant -- the pre-pandemic guideline and the pandemic

guideline, the mockup guideline -- say with regard to getting data in children?

The pandemic vaccine guideline says that in a pandemic children may be vulnerable to infection, and so constitute a special target group for vaccination. Once data from adults are obtained, it's recommended that at least limited data on safety are obtained from healthy children. In a pandemic, priority should be given to assessment of immunogenicity of the pandemic vaccine in children.

The pre-pandemic guideline says that studies in children and adolescents are needed to evaluate the immunogenicity and safety after acceptable data are obtained from healthy adults. In principle, it says the data are needed prior to licensure. Studies in infants and toddlers should be only initiated when data from all the children and adolescents have been found acceptable.

Both guidelines say the data in different age strata are needed, and they recommend a stepwise approach.

What is the EU experience with regard to pandemic and pre-pandemic vaccines? As I said, we do have to license or we do have to say no. We have three licensed pandemic vaccines at this moment. We have M59 and ASO3, and we have a whole virion cell culture-based -- whole virion vaccine -- licensed in the EU as pandemic vaccines, and we have a few in procedure at this moment.

Furthermore, we have one licensed pre-pandemic vaccine, and again we have a few in procedure. We have several at the stage of scientific advisers pre-submission.

It's very important that none of those licensed vaccines are licensed with pediatric data. There are no data in children in any of those dossiers. It's interesting, because the guidelines for the pre-pandemic dossier said that those data had to be there. But they are not. That also gives the difficulty.

Most important, of course, is to get the level of data that you would need. That's mainly driven by the level of the safety database that we request. That's completely different, as I always understand, from what the U.S. expectation is.

We have very limited expectations for these vaccines. This is for pre-pandemic vaccines. We ask for adults from 18 to 60 years old. They have to exclude rare events. They are defined by an incidence of less than 1 in 1,000 vaccinated. That comes up with a sample size of about 3,000 vaccinated subjects with the pre-pandemic formulation. For specific age groups or specific risk groups, the uncommon drug reactions have to be excluded, which means a sample size of about 300 individuals. As I already said, we still don't have the data in children.

So far, for the use of children to define pediatric requirements, we define children between the ages of zero to 18 years. We know that there are differences in

disease characteristics, immune responsiveness, and safety considerations. There are no data yet from pandemic or pre-pandemic licensed vaccines, but we also know that pre-pandemic trials have ethical limitations.

As you are here, we have also struggled with how to go forward. Maybe some of you know this picture, but maybe you don't. At this moment, many of us -- and I know the picture, so I know what to look for -- see a lot of white and black, but I hope that at a certain point we will see that there is a Dalmatian dog walking towards a tree in the snow.

That's actually where we should end: That we should somewhere see the picture on how to continue with pediatric data for pre-pandemic vaccines.

So now I'll get to very quickly what our ideas are on how to go forward. I must say, this is still an ongoing discussion. We have been discussing it. It's not finalized yet, so it may change. It may change because of discussions we have here. Maybe our views are helpful to your discussions here, but your views may also be helpful to our discussions.

So we have CHMP criteria for immunoprotection in adults and elderly for seasonal vaccines, but we use them also for the pre-pandemic and the core dossiers, the mockup vaccines, because we have nothing else at hand, and so we accepted the use of the CHMP criteria for adults and elderly.

For seasonal vaccines, as I said, we have no appropriate lab determinations. What we need is a pediatric plan for seasonal vaccines to establish the right dose and the number of injections. For that right dose and for those numbers of injections, we have to establish the efficacy and hopefully the correlates of protection, because that's what it's all about, and to use that information to get criteria for immunoprotection in children for seasonal vaccines, and not for pandemic or pre-pandemic vaccines.

If we establish that, we hope that we establish the criteria for immunoprotection as we use them now for adults and elderly, but for the pediatric population. That would mean that we have the same situation as I had four slides before, but for children, and a situation where it is ethical to do these clinical trials.

Further on, if we do the trials for pre-pandemic vaccines, we use those same pediatric criteria, considering the fact that those criteria are established based mainly on a non-adjuvanted influenza vaccine. The same holds for adults and elderly. But at least we have something in hand, and now we have nothing in hand.

So we use the pediatric criteria of immunoprotection for the pediatric plan, and the pediatric studies should establish the immunoprotection data, and especially the safety data.

For the pandemic vaccines, then we say that we don't need any further data, that we accept the experience from the pre-pandemic dossiers.

In conclusion, since 2002, when we started off the discussions on how to proceed with pre-pandemic and pandemic vaccines, we all knew that there was really a need for common research protocols. As you see now, you see some different studies. Everybody does something, but it doesn't bring you further. So there is a need for common research protocols. They will speed up the timely development of vaccines and also will help the common schedules and recommendations.

There is a clear need for pediatric data and criteria for pre-pandemic vaccines, but also for seasonal vaccines. At least for the European situation, installation of the Pediatric Committee has freed up this discussion and give us a powerful tool to go forward.

I think we all would benefit from harmonized regulatory requirements for pandemic or pre-pandemic vaccines for EMEA, FDA, WHO, and other regulatory bodies as necessary.

But for the EU perspective, at this moment, we are focusing on pre-pandemic and pandemic vaccines, but relying on the seasonal vaccines to pave the way. It may be too late, but we have had seven years of opportunity that we didn't take. We hope it's never too late to start at some point. So we decided to go forward at this point.

Now I want to add special thanks to Daniel Brasseur, who is the Chair of the Pediatric Committee, who provided me those beautiful last slides.

Thank you.

DR. MODLIN: Thanks, Dr. Voordouw.

We do have some time for questions. It was a very clear and informative presentation. Let's see if there are questions from the committee or anyone else, for that matter.

(No response)

I guess your presentation was so clear, there are none. So thank you very, very much. We certainly appreciate it.

The next presentation will be from Dr. Nelson, who, as advertised, will go through the Subpart D regulations in more detail for us.

**Agenda Item: 21 CFR Part 50 Subpart D --
Additional Safeguards for Children in Clinical
Investigations**

DR. NELSON: Good morning.

I'm basically going to walk through what has been referred to as the Subpart D regulations and provide an overview, as you start discussing today the scientific and ethical issues involved in the development of vaccines to prevent pandemic influenza in children. This presentation will introduce you to the pediatric research regulations

and the associated ethical principles which guide the design of pediatric clinical investigations.

It's important to note that this presentation is not intended to turn you into an IRB -- hopefully, that would not happen -- nor is it to have you function as a federal panel, which I'll get into at the end and point out the particular regulatory parameters around that panel, but simply to understand the ethical and regulatory parameters governing pediatric research to inform your discussion.

I'm going to cover the basic ethical framework initially and then walk through minimal risks and then what I call the ethical limits on pediatric risk, focusing on these two categories: minor increase over minimal risk, and then greater than minimal risk. I have given you the regulatory citations from 21 CFR 50. I'll end up with a brief discussion of the referrals under 50.54.

The basic ethical framework of pediatric research is that research involving children either must be restricted to minimal or low-risk absent a potential for direct benefit to the child. I have given you some citations to the CIOMS Guideline 9, the ICH good clinical practice guidelines, which use the word "low" and was actually the format for the European regulations that were put in place in 2001, and then given you the FDA citations.

So absent direct benefit, minimal or low risk. Then, if there is the possibility of anticipated direct benefit, the risks must be justified that direct

benefit. That risk/benefit balance must be at least as favorable as any available alternatives.

There is broad international consensus on this basic framework, although differences as to whether this is in a regulatory format or in a guidance format. The EMEA, for example, has a guidance that is similar to this, with some differences, given their regulatory context.

Let's start with minimal-risk research. I have put direct benefit, no direct benefit, and then the risk level, to give you a sense of the relationship. There's the citation. This is the definition: Minimal risk means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.

In the ethics literature, there is a large discussion of how you interpret this particular category. I should point out that the National Commission, which was the commission in the late 1970s that established this framework, defined minimal risks as those risks "normally encountered by healthy children." That phrase was not carried forward in the regulations. Although it's not included in the current definition, most ethicists and additional federal panels -- the Secretary's Advisory Committee for Human Research Protection, the Institute of Medicine -- agree with this interpretation.

"Routine immunization" was used as an example by the National Commission to illustrate this concept, but I would suggest that the administration of an experimental vaccine is neither routine nor minimal-risk. So I'm going to go on past that category.

The other two categories are minor increase over minimal risk and greater than minimal risk. I'm going to start with the minor increase over minimal risk. Basically, these really are the two options, as I mentioned before. If, in fact, your investigational product presents greater than minimal risk, either the risk must be no more than a minor increase, absent the direct benefit, or it must be justified by the potential for the product to directly benefit the child and for that balance of risk and benefit to be comparable to alternatives. Again, those are the two categories available to us at this point.

Let's talk initially about this "greater than minimal risk, no direct benefit" category, known as a minor increased risk. These are, in fact, the three criteria that you will find in that.

The first is that the risk is only a minor or slight increase over minimal risk. One could argue that this implies that you have some idea of what that risk might be, in order to place it into that category.

The second is that the experiences are reasonably commensurate with actual or expected situations. This was meant to inform parental permission and child assent,

although that as well is a point of discussion about how to interpret that category.

The final one is the yielding of generalizable knowledge of vital importance or understanding or amelioration of disorder or condition.

I'm going to talk a little bit in the next two slides about this "minor or slight increase over minimal risk" and then this notion of "disorder or condition."

A "minor increase" refers to a risk which, while it goes beyond the narrow boundaries of minimal risk, poses no significant threat to the child's health or well-being. I might point out, in the regulations themselves, there is no interpretation of "minor increase over minimal risk." What I'm giving you are quotations from the National Commission's discussion behind that category.

The second is, given this conservative limit, the promise of substantial future benefits to children other than the subject does justify research that goes beyond, but only slightly beyond, minimal risk. That was the intent of the Commission in offering this particular category.

What about "disorder or condition"? They didn't define it. They didn't define "condition" implicitly. You could argue that the notion of "disorder" was meant to be a disease. Again, the federal research regulations offer no definition either of "disorder or condition." The only proposed definition that is on the table at this point was

initially offered by the Institute of Medicine in 2004, modified slightly by the Secretary's advisory committee. I give you the IOM definition, which basically says it is a specific or set of specific characteristics that an established body of scientific evidence or clinical knowledge has shown to negatively affect children's health and well-being -- meaning now -- or to increase their risk of developing a health problem in the future. This notion of "at risk" I'll call your attention to, because I will expand on that a little further as I walk through the regulations.

Actually, I'll expand on it now.

Healthy children: In the vaccine arena, there is a lot of use of the term "healthy children." The word "healthy" is not used anywhere in 21 CFR 50 and 56. I suspect, although I didn't do the research, that it's not found anywhere in FDA regulations at all -- but I'm not going to back that up with data at this point -- and can be misleading. A child can be healthy and at risk, which is a notion of having a condition. A child with a condition may not have the condition related to the research, and thus could be healthy relative to that research.

So my recommendation is that a more accurate designation, rather than using the word "healthy," would be children with the disorder or the disease, or who are at risk for the condition which is the object of the research, or children without the disorder or disease or without

being at risk, without having the "at risk" condition which is the object of the research.

The word "healthy," I think, is problematic, because often it's not clear which of those two definitions is being used at that time.

Let's talk now about this "greater than minimal risk, prospect of direct benefit" category, which is 21 CFR 50.52. Here are the criteria for approval, which you have heard before:

- The risk is justified by anticipated direct benefit to subjects within each arm of the study.
- The relationship of anticipated direct benefit to risk is at least as favorable as available alternative approaches.

Let's talk a little bit about "prospect of direct benefit." Very simply, the notion about a benefit being direct could be seen as it's my benefit, not your benefit. It's a direct benefit to me, and not you, when you enroll me in the research. It results from the research intervention being studied, and not necessarily from incorporating other interventions into that protocol. Otherwise, we could fill up research protocols with a lot of health care and use that to justify the research risk of the intervention that is being studied. That's referred to as "the fallacy of the package deal."

So the word "benefit" is often modified by "clinical" to indicate that direct benefit relates to the health of the enrolled subject.

I might also point out that the notion of "prospect of direct benefit" is based on the structure of the intervention -- in other words, what's the evidence in support of that? -- rather than simply the intent of the investigator to say, "I think this is going to provide some benefit."

I might point out, though, that the evidence in supporting the prospect of direct benefit would be weaker than evidence supporting efficacy. Otherwise, we end up in a circular situation: We can't initiate a pediatric trial until we have efficacy data, which is a nonsensical position. So whatever evidence one brings to bear on this notion of "prospect of direct benefit" would necessarily be weaker than evidence that you would expect for efficacy.

You may well base this on a surrogate endpoint, which is a large part of the discussion in this arena -- immune response, which was illustrated nicely, I think, in the previous presentation. But again, what evidence do you have linking this chosen surrogate to clinical efficacy, which is, at the end of the day, what you are fundamentally interested in?

Here's where the link to this notion of "condition," under 50.53, is important. Whether a child may directly benefit from an intervention that prevents

disease depends on whether that particular child is at risk for developing the disease in the future. Otherwise, there is no benefit of prevention, if you are not at risk for that disease. Thus, for a preventive intervention, both 21 CFR 50.52 -- in other words, the category that is directed at those interventions that offer the prospect of direct benefit -- and 50.53, which has the explicit language of "disorder or condition" -- both require the child enrolled in the research to have the condition of being at risk for future disease.

In addition, 21 CFR 50.52 has this other language about the comparability of the risk and benefit. But both of them have this implicit notion of being at risk in the context of a preventive intervention.

It raises the issue about who is at risk for H5N1 influenza. This is simply a picture of the data that Douglas showed you earlier, to just illustrate this question. It's not intended to answer the question. You are the ones that are going to have to answer this question.

I might point out, though, in applying the research regulations, the relevant population that is thought to be at risk, those who may be at risk for the disease, are the children that are enrolled in that particular protocol. So when we use the "at risk" language, it's the children enrolled in that protocol that are the at-risk population that would be the focus of discussion for the purpose of the research regulations and guidelines.

Let me finish up with this notion of IRB referrals under 50.54. You saw the previous illustration that Douglas gave you for the smallpox vaccine. I might point out that that referral came in before the process I'm going to show you was, in fact, set up, since the Pediatric Advisory Committee did not exist at the time of that smallpox example.

An IRB may refer research involving children which does not meet 50.51-53 for federal review. The IRB is supposed to feel that the protocol is worth doing and would be a reasonable opportunity. But as mentioned, this research may proceed only if the FDA Commissioner, after consulting a panel of experts, and following public review and comment, determines either that one of the other categories is met and that the IRB referral actually was, to some extent, unnecessary -- that one of the other three categories applies -- or that indeed it presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health and welfare of children and will be conducted in accord with sound ethical principles. As mentioned, the Pediatric Advisory Committee, which does have a permanent Pediatric Ethics Subcommittee as part of its structure, is by its charter the one that makes these recommendations to the Commissioner.

But let me show you some language in the National Commission's report about why they thought it was

worth setting up this process in the first place, which is seen as exceptions to this general framework. They recognized that, "In exceptional situations, dangers to children or the community resulting from a failure to involve children in research might exceed whatever risk is presented by that research. For instance, the threat of an epidemic that could be offset by developing a safe and effective vaccine might justify research involving risk greater than otherwise acceptable to establish safety, efficacy, and dosage levels for children of different ages."

That's a direct quote, 1977.

They went on to say, "The ethical principles at stake are the moral obligation to protect the community or to come to the aid of certain sufferers within it and the moral prohibition against using unconsenting persons, at considerable risk to their well-being, for the promotion of the common good. These principles are of such moment and their observance so basic to a just and humane society that any debate about their application should be held at the most public level of discourse."

Here you are: Even if you are not a panel, you are at least participating in that public level of discourse.

Let me leave you with a summary of this basic ethical framework, again with that question raised by the National Commission about exceptions to that

framework: Risk involving children either must be restricted to minimal or low risk absent the prospect of direct benefit to the child, or must present risks justified by anticipated direct benefits to the child, and which are as favorable as any available alternatives -- again, with the question as to whether or not the research that you are being asked to ponder today fits within this framework or is an exception to that which could be conducted nevertheless.

With that, I thank you.

DR. MODLIN: Thanks, Dr. Nelson.

Let's ask if there are questions for Dr. Nelson, or comments. If anyone would like to discuss any of these issues, this would certainly be the time to do it, before we get into the more technical discussions a little bit later on.

Dr. Joffe?

DR. JOFFE: Thanks, Skip, for a terrific presentation. I want to just get you to say a bit more about the notion of a condition, who has a condition, and whether individuals who are at risk, particularly when that risk is spread population-wide, as I think it is in this case, can be considered to have a condition.

Thinking back to the SACHRP recommendations, which I didn't review specifically in advance of this meeting, I seem to remember -- and you will remember better than I do -- that they left open the possibility that the

entire population of children -- I'm thinking about the pediatric recommendations from SACHRP -- the entire population of children could be viewed as having a condition by virtue of being at risk for something that might strike anybody in the population, and vaccines would be a prime example.

Can you clarify a bit more? You hinted that there were some subtle differences between the IOM recommendations and the SACHRP recommendations. Your slide from IOM suggested that one would need to have defined high-risk groups, as opposed to a population-wide view of being at risk for a condition. Can you say a bit more about that?

DR. NELSON: My comment about the subtle differences was not directed at that point. I think, consistent with the IOM recommendation, one could decide that a population is at risk as opposed to individuals within that population. I think one could think of examples of diseases where, if we fail to immunize the entire population up to a certain level of herd immunity, in fact we all would be susceptible to that disease. Measles might be one. There was, in fact, a case of measles at the University of Pennsylvania just the other day, among graduate students. So everyone is at risk that was in that building. So I think that would be very different.

The only difference in the definition was, there was a concern about using socioeconomic and other variables to place populations at risk. So they added something about living in a healthy environment, to try to address some of those issues. But it leaves open the interpretation. "Healthy environment" wouldn't necessarily mean that you are not at risk for the diseases that might exist. Obviously, diseases vary, depending upon the part of the world that you live in.

So I think that is an open question that it would be interesting to hear everyone's thoughts on in the course of the day.

DR. MODLIN: Seth?

DR. HETHERINGTON: I wonder if you would, on slide 14, expand a little bit on one of the statements there, something to do with risks justified by anticipated direct benefit to subjects. Then in parentheses it says "within each arm of the study." How do you interpret that? Can you expand on that in the context of a placebo-controlled trial, where one arm of your subjects are not going to get any potential direct benefit if they are assigned to a true placebo. How does this fit in?

DR. NELSON: Briefly -- that was a whole topic of discussion at an Ethics Subcommittee meeting last June -- the notion of the placebo-group risk is one approach to that. Again, I'm not saying the regulations drive this approach. But one interpretation that would be consistent

with this is that the risk to the placebo group is driven more by what they are not getting than it is by the risk of the placebo, so that you would limit the risk to that group to a minor increase over minimal risk, which is then more related to the question of what they would not be getting if they are not getting their experimental product. One certainly wouldn't have a placebo control that would be considered risky.

That's very separate from adding other vaccines in as controls, which I think are based on more the virtues of providing some active vaccine to the control population, as is often performed, say, with either a rabies vaccine or MMR or something that would be appropriate for that population. It's not really a placebo-controlled trial, strictly speaking.

DR. HETHERINGTON: What about the procedures of participation in a protocol -- for instance, phlebotomy done on a routine basis for some interval of time, which I think represents more than the risk that a child would encounter as daily living? How does that fit into this?

DR. NELSON: I think most IRBs -- there are some differences of opinion, I think, but most IRBs would consider a certain amount of blood testing to fit within the minimal-risk definition.

DR. MODLIN: Bob?

DR. DAUM: Skip, thank you for a nice, informative presentation. I want to ask a question, where

I sort of already know the answer, but I would like to hear you reflect on it. The situation where the IRB has deemed that it cannot rule and needs to go through the federal process that you outlined involving the Pediatric Advisory Committee -- could you just tell us what your current view is on how long that process takes? You could do it from the time you submit to the IRB or from several months later when the IRB actually realizes that it can't decide and needs to punt to the federal process.

DR. NELSON: Let me just go through the steps, because for me to say what I hope would happen versus what actually happens, I think, would not be useful. The steps would be the IRB referral process and then the acceptance, which becomes a little more complicated, as it was in the smallpox context of HHS-funded and FDA-regulated. Then it ends up as a collaborative process with the Office for Human Research Protections at HHS. At that point, obviously, we need to pull the panel together, which is the Ethics Subcommittee. Subcommittees cannot advise the Commissioner, so the Pediatric Advisory Committee then has to meet as well. That committee meets routinely three to four times a year, and some of the timeframe is the timing between when the next meeting is and when the referral comes in and how quickly we can get that process going.

After that, depending on the panel's recommendations, we generate a letter of the FDA Commissioner's determination, which, if it was not HHS-

funded, would be the final step; if it is HHS-funded, the next step would be to go to OHRP, who would then write a letter to the Assistant Secretary for Health.

So that process -- I guess we can all speculate about how long it takes, but it has generally been on the order of six to 12 months.

DR. DAUM: Wouldn't you agree that sometimes it has actually been quite a lot longer than that?

DR. NELSON: Well, one could say the smallpox determination is still not made. But that was withdrawn by NIH because they decided to go in a different direction. But the determination on that one, I don't think, was ever actually made, to my knowledge.

DR. MODLIN: Dr. Fost?

DR. FOST: Just one brief comment on that and then another comment.

By the chair, I'm Chair of the Pediatric Ethics Subcommittee.

In some of the cases that went very long, it was at the local institution. That is, it took them a year to get their act together and debate whether to send it in or not, getting their materials together, and so on.

DR. DAUM: I totally agree with that, but long is long.

DR. FOST: Yes. I just want to go back to the subject's-condition issue. I'll come back to this later. I don't think it's necessary to go to that part of

the regulations to approve the trials that we are talking about. But suppose one were in 50.52 and one had to decide whether the subject's condition applied. I think it's important to remember why that is in there -- that is, the ethical reason for requiring that the subject must have the condition that you are doing the research on. This is a category, remember, for research that has no prospect of direct benefit. I don't think that's true with these vaccines, but let's suppose you are talking about such a study. The idea here is that since the child can't, himself or herself, consent, you are trying to make a guess about whether he or she would if they had a moment of lucidity and was fully informed.

This was Richard McCormick's argument: That the child, if it was about his condition, he probably would consent, because he would want knowledge to advance about his or her condition.

If that's the reason for it, if that's the moral basis for requiring that it be about the child's condition, then children who are at risk for this kind of highly fatal flu -- it's not hard to construct an argument that, of course, they would want reasonable research, well-designed research, to go on that would protect them from this.

DR. MODLIN: Dr. Debold?

DR. DEBOLD: Going back to slide 14 again, you mentioned risk to the placebo group if they were getting another vaccine that could potentially confer

benefits. What about the situation where the placebo is actually the adjuvant, which may not, in fact, confer benefits at all, but increases their exposure to risk of adverse events?

DR. NELSON: I have never been asked that question before, and I'm a little loath to just give an off-the-cuff answer. But I think you would have to evaluate the risk/benefit to that group where you are giving them the adjuvant without the antigen. I think it's a reasonable question. Without getting into the details on the data, I usually don't even answer questions like that off the cuff internal to the FDA, and I'll doubt I will do it external, without getting into the data as well.

But that would be a question that would have to be addressed.

DR. MODLIN: I could take a quick shot at that. It may very well depend on the value of the data. The overall understanding of the use and application of the vaccine to that population would be the question, I think, that would need to be asked.

Dr. Nelson, let me ask you whether or not you or the agency considers the decision that was made with respect to smallpox vaccine to have in any way set a precedent, not necessarily in the legal sense, but that it does provide at least a precedent that we can work from in making these decisions as we go forward, with not only this

vaccine, but perhaps other vaccines that are being tested in children in similar situations?

DR. NELSON: No.

DR. MODLIN: Dr. Joffe?

DR. JOFFE: I just want to make a comment in response to a question that Dr. Hetherington raised a little while ago with respect to the blood draws and other procedures that might involved in a study like this and whether those -- setting aside the exposure to the vaccine -- might be considered minimal risk.

In the regulations from OHRP, there is a set of criteria for what can be reviewed in an expedited fashion by an IRB. One criterion is that the study has to involve minimal risk. Then there are, I think, eight specific categories of studies that can be reviewed in an expedited fashion and don't have to go to a full board. One of those categories is studies involving blood draws in children, presuming that they meet certain thresholds of blood volume. So within certain bounds, they can be considered minimal risk.

So that's already in OHRP's guidelines and may be helpful in realizing that at least some studies that involve just the blood draws might fall into the minimal-risk criterion. That already seems to be accepted in guidance and regulation.

DR. MODLIN: Any other questions or comments?

DR. NELSON: Let me just give one clarifying comment to Steve's remarks. The expedited criteria are, in fact, in FDA's acceptance as well. What it says is that it needs to be both minimal risk and on that list. It's possible that an IRB might decide that being on that list doesn't make it minimal risk, but I think it's fair to say that the overlap between minimal-risk determinations and being on that list is probably nearly 100 percent.

DR. MODLIN: Thank you. Bob?

DR. DAUM: I would like to ask Skip to reflect on one other issue that I have been thinking about. It goes to the map of the world that you showed, with the cases of H5N1 that are currently known in humans. It also seems to me that one of the things that may be on the table here, but not said, is, is there a risk to children of H5N1 virus spreading this week, next week, this year, next year? Of course, the magnitude of that fear, threat -- I don't know what the right word to use is -- is not known. But it seems to me that it's a number that is not zero, in our minds. Otherwise, we wouldn't be sitting here discussing this. In other words, the whole discussion of whether we want to test H5N1 vaccines for a total theoretical idea that no one has ever thought about, has never happened before, couldn't possibly happen here -- we wouldn't be discussing that.

So we all must believe, at some level, that there is some admittedly indefinable threat of this virus coming

to children in our country and European countries in the world. It's that risk of disease -- not risk of procedure, but risk of disease -- that, it seems to me, is driving this discussion to a fair extent. We don't say that enough, because it goes to how we categorize the research, believing that there would be benefit if there is a risk of the virus coming and there would be no benefit if there is no risk of the virus coming.

Do you see where I'm going? I would really like to hear your comments on that. Just showing us a map like that, implying that there aren't any cases here, and therefore there is no concern, which I know isn't what you mean -- how do you deal in your deliberations about this with the level of concern of the virus coming, and therefore the need to protect our children?

DR. NELSON: I think that's the question this committee is being asked to discuss. That map was simply a reflection of existing, current cases. It has nothing to do with the determination of risk, which is future cases.

DR. MODLIN: That's why we're here.

Any other comments?

(No response)

If not, I would like to thank Dr. Nelson for a very clear and helpful framework. It does provide a nice framework as we continue on with our discussions.

We are about 30 minutes ahead. I would like to suggest that we go ahead and take our break now. Let's

return at 10:30 sharp, if we can, with the manufacturers' presentations.

(Brief recess)

DR. MODLIN: We come to the next portion of the meeting, which will be a series of presentations from influenza vaccine manufacturers. The first presentation will be by Dr. David Vaughn, from GlaxoSmithKline.

Agenda Item: GlaxoSmithKline Presentation

DR. VAUGHN: Good morning. Thank you for this opportunity to present GSK data for children who have received adjuvanted H5N1 vaccines and to provide a rationale for continued testing in children.

I hope you will understand that it's a little bit awkward for manufacturers to be presenting data on clinical trials in children so that you can decide if it's appropriate to conduct clinical trials in children. But we will do the best we can.

My presentation will touch on the following topics: First, indeed, children do suffer from interpandemic and pandemic influenza, and vaccination, for the most part, protects them. We will want to vaccinate children during the next pandemic, as outlined in this guidance document from HHS. However, the next pandemic could occur very quickly, with little time to test vaccines in children. It is the position of GSK that limited testing of pandemic vaccines in children should occur during the pre-pandemic period. This data could be very

beneficial to pandemic planners, and perhaps reassuring to public health decision makers, health-care providers, and parents, to be working with a licensed vaccine with an indication for use in children, rather than to be working under an emergency-use authorization.

GSK and other companies have already conducted some trials of adjuvanted H5N1 vaccines in adults and children, and we will present some of that data this morning.

GSK believes that an ethical framework does exist for continued testing in children.

Influenza, as has already been pointed out, is common in children, even in non-pandemic years. Each year, 15 to 42 percent of preschool and school-age children are infected with virus. Of course, not all of them become ill, but many do. Hospitalization rates for children under 2 years of age are similar to those for adults 65 years of age and older -- as high as 450 per 100,000 in children in the first six months of life, 4 to 21 times higher for children with underlying chronic medical conditions. Of course, there are many more outpatient visits, 10 to 250 times more.

Fortunately, deaths from influenza in children are unusual, but they do occur, at estimated rates of around 2 per 100,000 for infants in the first year of life.

Chris Potter reports that there have been nine pandemics in modern times, meaning from 1700. There will

be another influenza pandemic. We do not know when, we do not know the subtype, and we do know the severity. The 1918 pandemic was particularly rapid and lethal. Two percent of those who became ill died. There were an estimated 50 million people, ultimately, who died during this pandemic, two-thirds of whom died over approximately a six-month period.

If you look at this graphic from Dr. Potter's publication, you will notice that there is an axis break here at 3.5 million deaths. To capture this peak in 1918, this graphic would need to be 14 times taller than is shown here.

In terms of the impact of the 1918 pandemic on children, Alice Reid has reported recently that infant mortality increased by 50 percent in Derbyshire, England in 1918. That's compared to 1917 and 1919 to 1922. Denmark reported peak disease incidence in children 5 to 15 years of age, though mortality was highest in the children in the first year of life and in young adults, 20 to 34 years of age.

The pandemics in 1957 and 1968 were much milder by comparison. But even here, children were three to five times more likely to get sick than their parents or adults the age of their parents.

While we do not know which subtype of influenza A virus will cause the next pandemic, the current concern is H5N1, obviously, the reason for this meeting today. This

graphic has already been shown. We know that approximately half of cases have occurred in children and that the mortality has been extremely high, in excess of 70 percent for children 10 to 19 years of age. We don't know why there are more children affected. It could be that they are more susceptible to infection, it could be increased risk of exposure to H5N1 virus, or perhaps there is some relative resistance to infection among older adults. Of course, it could be some combination of these.

A public health official's worst nightmare has to be an influenza pandemic caused by a virus with the transmissibility of the 1918 H1N1 virus and the lethality of the current H5N1 virus.

Regardless of the disease burden, we need to have some assurances that vaccination will provide some protection. I won't go through the details here. Whereas individual clinical trials to look at efficacy in children vary in terms of the results, there have been several meta-analyses that consistently show the benefit to vaccination and serve as the basis for current ACIP and AAP recommendations for yearly vaccination of children.

Vaccines not only protect children in the seasonal setting, but since children play a central role in the spread of influenza, also protect the greater community. Children are more susceptible to infection. They shed virus at high titer and for longer

periods, up 10 to 14 days. Once they start walking, they are socially mobile and highly interactive.

Models my wife ran all suggest that vaccinating 20 percent of children in a community would reduce the amount of disease across all age groups by 46 percent; vaccinating 80 percent of children would reduce total cases by 91 percent.

I'm sure VRBPAC members are all very familiar with the movie that this graphic represents. It dramatically makes the point that there may not be adequate time for pediatric trials once a pandemic begins.

I won't go into the specifics of this particular scenario, but just point out that the models suggest that virus may circulate in the United States unrecognized for 24 days and then increase dramatically in terms of frequency, up to 4.5 million new cases in a single day, just 61 days later.

Neil Ferguson suggests that a pandemic that starts anywhere in the world could be in the United States within one month. So we may be talking only about a four-month period before much of this is over with. If it takes four to six months to produce the first doses of strain-specific vaccine, you can appreciate the problem.

The good news is in the lower graphic, where the rapid deployment of a stockpiled vaccine, even if of modest efficacy, could dramatically change the outcome, particularly if children are targeted for vaccination.

As a part of GSK contributions to pandemic preparedness, GSK is utilizing alpha-tocopherol-based adjuvant system number 3, or ASO3, in combination with hemagglutinin antigen, using conventional production processes. We make the antigen in two sites. The D-Pan antigen is manufactured in Dresden, Germany, "D" for "Dresden," using the Fluarix process, which is licensed in the U.S. To date, we have safety data in more than 5,600 adults and 300 children aged 3 to 9 years. We will turn to that data momentarily.

This vaccine has been licensed in Europe, registered as Pandemrix, as a mockup vaccine for use during a pandemic, and Prepandrix for pre-pandemic use.

Q-Pan antigen is produced in Quebec Province of Canada using the FluLaval process. We have safety data in more than 3,600 adults. This vaccine has been shown to be immunogenically equivalent to D-Pan.

The potency of this vaccine comes from the adjuvant ASO3, which results in an antigen-sparing vaccine, at least 24-fold. This means that rather than using 90 µg of antigen only twice, we can use 3.8 µg of antigen. In theory, this could take the current 12.2 million courses of vaccine reported by Secretary Leavitt to be present in the U.S. stockpile as of September 2008 and extend that to 292 million courses of vaccine, approaching the population of the United States. As I will mention in a moment, we

anticipate that the dose for use in children will be 1.9 µg of antigen, which would extend the stockpile even further.

With the adjuvant, the vaccine is highly immunogenic in adults 75 years of age and old. It prolongs the duration of measurable antibody. A single dose primes for a later robust anamnestic response many months later. In humans, we see cross-reacted antibody generated, both in terms of hemagglutination inhibition antibody and neutralizing antibody.

While we won't have protective efficacy data in people until a pandemic occurs, there is an animal model, ferrets. We are able to demonstrate cross-clade protection in ferrets. That is, if you vaccinate them with a clade 1 antigen vaccine and then later challenge them with a clade 2 wild-type virus, they are protected.

GSK anticipates submitting a BLA for Q-Pan this year. The indication that we will be seeking will be for use in adults at increased risk of exposure to H5N1 virus. The submission will be based on the following:

- First, dose-selection studies using D-Pan and Q-Pan.

- A demonstration that Q-Pan is highly immunogenic, both in adults 18 to 64 years of age and in adults 65 years of age and older.

- There will be Q-Pan-specific safety data for more than 3,600 adults and more than 1,000 adults 65 years of age and older.

- An integrated summary of safety that will look at pooled data from D-Pan studies and Q-Pan studies.

While there is a large safety experience with inactivated split influenza antigens in children 6 months of age and older, there is currently very limited pediatric safety experience using the AS03 adjuvant. European regulatory authorities, as we heard this morning, have determined that these vaccines should be evaluated in children, including infants, and should include an evaluation of the effectiveness of boosting. The viewpoint in the United States has been quite similar, at least until this morning. We have contracted by HHS to conduct pediatric trials with Q-Pan.

Let's turn to the data now. Following the completion of several D-Pan vaccine assessments in adults, GSK conducted a preliminary study, under U.S. IND, in 405 children aged 3 to 9 years. This was conducted in Spain in 2007 and 2008. The virus antigen used was A/Vietnam, a clade 1 virus. Each formulation -- and there were three -- was first tested in children 6 to 9 years of age and then, in consultation with an independent data-monitoring committee, or IDMC, also tested in children 3 to 5 years of age. By the end of the trial, 300 children had received H5N1 vaccine, D-Pan, and 105 children had received two doses of Fluarix as an active control.

The following slides will have data only from Phase A, which has previously been publicly disclosed. But there were three phases, Phases A, B, and C.

In Phase A, children received half the standard amount of hemagglutinin antigen and half the standard content of the adjuvant AS03, which we refer to here as AS03B. In Phase B, children received the standard amount of antigen and AS03B. In Phase C, children received the standard amounts of antigen and adjuvant.

These green arrows indicate where the study advanced in consultation with the IDMC.

Based on the hemagglutination inhibition assay, the D-Pan vaccine was highly immunogenic. The data here is the proportion of subjects who had HI titers of 1 to 40 or greater. This is an HI level thought to be associated with benefit and in this particular study is synonymous with seroconversion rate, as all the children were seronegative at the onset of the study.

On the left half we have data using an HI assay with homologous HI antigen, A/Vietnam, clade 1, and on the right half, using heterologous antigen, A/Indonesia, clade 2.1. We have data for children 3 to 5 years of age and 6 to 9 years of age.

For the children 6 to 9 years of age who received Fluarix, there was no immune response to the H5N1 HI assay. For children who received the D-Pan product, 30 percent seroconverted by day 21 and 100 percent

seroconverted by day 42, 21 days after the second dose of vaccine, which was given on day 21.

For children 3 to 5 years of age, 12 percent seroconverted by day 21 and 96 percent by day 42.

In an assay using heterologous antigen, the seroconversion rates were 71 percent and 74 percent.

Immune responses across clades support the preparedness strategy of stockpiling.

In terms of geometric mean titers for the children 3 to 5 years of age, GMTs were around 1 to 400, and for the slightly older children, in excess of 1 to 500. When tested using heterologous antigen, the GMTs dropped by about a log to about 1 to 60, which is still about 10 times higher than baseline.

Solicited local symptoms were similar between D-Pan recipients and Fluarix recipients, with the exception of injection-site pain, in the center of this fairly complicated graphic. This has also been seen in our adult studies. Subjects are much more likely to complain of injection-site pain with this adjuvanted vaccine.

For children 6 to 9 years of age who received D-Pan, 86 percent complained of injection-site pain, compared to 67 percent of subjects who received Fluarix. In the 3- to 5-year-old children, 61 percent complained of injection-site pain compared to 39 percent of those who received Fluarix in that age group.

There were some grade 3 complaints of pain in the D-Pan recipients and none in the Fluarix recipients. This is similar to what we see in the adult studies, with the possible exception that in adult studies where we give antigen only or even saline placebo, we usually see grade 3 complaints in 2 or 3 percent of adult subjects.

The duration of this injection-site pain -- the mean was two days in both the D-Pan group and the Fluarix group, meaning they complained of pain on the day of inoculation and then the next day, on average.

Complaints of general symptoms were fairly homogeneous between groups for the 6- to 9-year-olds. In the 3- to 5-year-olds, while overall the numbers of complaints were low, there were more in the D-Pan group than in the Fluarix group.

The IDMC did not raise any safety concerns throughout this trial. There were no SAEs in Phase A. Until recently, there were no SAEs in any phase of this trial. There was one SAE reported in a child who had elevated liver enzymes on day 0, the day of vaccination, prior to vaccination. Eleven months later, this child underwent liver biopsy for continued elevations, and a diagnosis of autoimmune hepatitis was made. This child has remained asymptomatic throughout this time, but still, as of February, this month, he does have elevated liver enzymes.

That's D-Pan data.

GSK suggests that a Q-Pan pediatric protocol can be appropriately reviewed by IRBs in alignment with Title XXI, CFR Part 50, as was discussed earlier this morning. It's possible that an IRB could review such a protocol under Subpart 50.52, meaning they think the risk of an H5N1 pandemic is real and that HI antibody suggests the possibility of protection, or at least solid priming for protection with a subsequent dose.

However, we do not have definitive efficacy data for this vaccine, and we won't until there is a pandemic. Currently, highly pathogenic H5N1 virus is not circulating in North America. So other IRBs may want to review this protocol under Subpart 50.53 or 50.54.

What I have on this slide is an outline of thoughts under 50.53. As we heard, there are four regulatory requirements:

First, the risk to study subjects must represent only a minor increase over minimal risk. This assessment could be made by the IRB, based on more than 9,000 adults who have been exposed to this type of vaccine. What is expected is self-limited, short-term reactogenicity.

Second, study subjects' experiences in the trial must be reasonably commensurate with those inherent in their actual medical situation. Again, this the "healthy children" discussion, where they routinely receive childhood immunizations, some of which are fairly

reactogenic, and venipuncture is also a fairly common childhood experience.

Third, the study must be likely to yield generalizable knowledge that is vital to the amelioration of the condition. Here we have the discussion of what is the condition. Some would say that children in North America are not at risk for H5N1 infection. The counterargument would be that the condition is susceptibility to an influenza pandemic, a condition that we all share.

There is the opportunity, if the studies are conducted in advance of a pandemic, to demonstrate that the vaccine is immunogenic in children, and therefore potentially protective. It gives us an opportunity to identify a proper dose. Also it reduces the risks associated with exposure to an untried pandemic vaccine. If we are talking about 61 days to the peak of the pandemic, we will want to vaccinate very quickly once the pandemic is declared, perhaps unless less than ideal circumstances.

Finally, adequate provisions must be made to solicit the assent of the children and the permission or consent of their parents or guardians.

To conclude, I would like to emphasize a few points:

- First, children in the United States will be among the first to receive pandemic vaccines, in agreement with the HHS pandemic plan.

- Second, a conventional inactivated antigen approach may not meet the public health needs.

- There are potential benefits to the use of adjuvanted vaccines to address a pandemic. These include enhanced cross-protection, enhanced priming of immunity, and, because of antigen-sparing, the ability to rapidly deliver to all U.S. citizens, including children, vaccine.

- GSK believes that the initiation of carefully planned and well-controlled clinical trials of novel pandemic vaccines is ethically appropriate and in the U.S. public's best interest.

Thank you.

DR. MODLIN: Thank you, Dr. Vaughn.

We have time for one or two quick questions. Dr. Fost?

DR. FOST: Dr. Vaughn, with regard to the prospect of benefit, that would be highest in the areas where the risk of getting this kind of flu is highest. That would argue for doing the trials in the highest-risk countries, in Asia, et cetera. Do you agree with that, that there is an argument for doing the trials in the highest-risk areas?

DR. VAUGHN: There have been approximately 200 children who have suffered, many who have died, in at-risk

regions. I'm not sure how high that risk is, even there. We are focused on seeking a licensure in the United States, so the FDA may want to see data in children from this region.

But, yes, a study could be conducted in other areas.

DR. MODLIN: Ted?

DR. EICKHOFF: Dr. Vaughn, could you reiterate what you said about duration of local and systemic symptoms, particularly the injection-site pain issue?

DR. VAUGHN: What I said was that for this pediatric study, the mean duration of injection-site pain was 2.1 days. This was both for D-Pan recipients and for Fluarix recipients. Two days would mean the day of inoculation and the next day. That would be the average. The other half of the children would complain of injection-site pain on the third day, maybe 48 hours after injection.

DR. EICKHOFF: Were parents instructed to treat injection-site pain in any fashion?

DR. VAUGHN: I don't know the specifics of that. I imagine that they were not given specific instructions to treat, but they certainly would be free to treat with paracetamol or acetaminophen.

DR. MODLIN: These immunization protocols often include specific recommendations for management of injection-site reactions.

DR. VAUGHN: There was no prophylactic administration. In fact, it's an exclusion criteria if children receive prophylactic medication on the day of vaccination.

DR. MODLIN: José?

DR. ROMERO: A question and a comment. Could you tell us about the fever? Was the magnitude of fever in the group that received the H5N1 vaccine higher than that in the group that received Fluarix?

The comment is, soliciting headache in this age group is a difficult symptom to elicit. There was a large meningitis trial study that failed to reach significance, in part because that symptom is very hard to elicit in that age group. That's the comment.

DR. VAUGHN: In terms of fever, there was actually more fever among Fluarix recipients -- slightly more -- than among D-Pan recipients in the 6- to 9-year-olds. For 3- to 5-year-olds, there was no fever in the Fluarix group, but about the same frequency of fever in the D-Pan group as in the 6- to 9-year-olds.

In terms of headache, yes, it can be difficult to elicit that. We only ask that question to 6- to 9-year-olds. That question was not asked to 3- to 5-year-olds, though it could be an unsolicited complaint.

DR. ROMERO: Let me just follow up. Perhaps I didn't explain the question well enough on fever. Was the magnitude of fever -- that is, how many kids had fever

greater than 102 or 103, significant fevers -- in the two groups, were they comparable or were they not comparable?

DR. VAUGHN: There was grade 3 fever in a Fluarix recipient or two. I believe that is 39 degrees or higher. No fever over 39 degrees among D-Pan recipients. It looks like there was one in the 3- to 5-year-old age group.

DR. MODLIN: Dr. Debold?

DR. DEBOLD: The adjuvant, ASO3, would be new to the United States. It's something that we haven't used in vaccines here. I understand that it contains squalene.

DR. VAUGHN: Yes.

DR. DEBOLD: And I understand that one of the concerns with those products is the potential for autoimmune illnesses, responses. This was, as I understand it from reading the documents that were provided to us, a relatively small study in children. To have one child out of about 100 with autoimmune hepatitis is something that I find concerning.

Can you talk a little bit about preclinical-trial information about this adjuvant, the extent to which you actually have experience with it in children?

DR. VAUGHN: I might just comment on the autoimmune hepatitis case. That was a preexisting condition, in that the child had elevated liver enzymes prior to the study's start.

In terms of the squalene issue, I think that has been maybe of less importance since the WHO comment on it in 2006. They felt that concerns about squalene were unfounded. That was their final assessment, at the end of that publication. That was largely based on Novartis studies with MF59, which also contains squalene -- to not see an increase in anti-squalene antibodies in those subjects.

The last question was about our safety experience with ASO3 in children. You have seen it -- 300 children.

DR. MODLIN: Lisa, do you have a question?

DR. JACKSON: Just a point of clarification. The D-Pan pediatric trial was 300 total or Phase A was 300? The data we are looking at are from how many --

DR. VAUGHN: The total trial was 300. Phase A was 101 children.

DR. MODLIN: Roland?

DR. LEVANDOWSKI: Just one quick technical question on that study design. There is both ASO3B and ASO3A. I didn't quite catch what the difference between those was, why the study population -- you needed to do those two cells for those two different types of ASO3.

DR. VAUGHN: The ASO3 in this study is a simple one-to-one dilution of the standard concentration of ASO3. It's half the content of the active components, the alpha-tocopherol and the squalene.

DR. LEVANDOWSKI: And that's the difference between the B and the A?

DR. VAUGHN: Yes.

DR. LEVANDOWSKI: I see.

DR. MODLIN: Pam?

DR. MCINNES: I'm interested in your study age groupings -- just on this quick look, really not seeing differences in either safety or in immunogenicity that look meaningful between the 3- to 5-year group and the 6- to 9-year group. I think it's a very conservative approach that you took in terms of step-down. Do you think, if you were to do it again, you would feel you could now put 3- to 9-year-olds together, 2- to 9-year-olds together? What is the thinking about it?

DR. VAUGHN: The division in age here is largely due to the maturity of the child. We have different adverse events that we solicit in the younger age groups. That's why the data is presented separately. Now that we do have data in 300 children -- it would depend on the IRB and the regulatory authorities that we consult with, but, yes, I would think we could do that entire age range in a single study.

DR. MCINNES: So 3 was the youngest?

DR. VAUGHN: Yes.

DR. MCINNES: We normally think about 6 months to 2 years old. What was the thinking about 3?

DR. VAUGHN: This follows roughly the thinking for seasonal vaccine, where you use a smaller dose in children under 3. From children 3 to 8, you use two doses, and so on. So it roughly follows the age breakdowns in the recommendations for seasonal flu.

DR. MODLIN: Dr. Gilbert?

DR. GILBERT: Given the possibility -- and maybe likelihood, from what I'm hearing -- that a pandemic strain might be antigenically mismatched to a pre-pandemic vaccine, I'm interested in the issue of developing a standardized panel of avian flu isolates to evaluate. I suppose, ideally, that panel would be representative of the spectrum of strains that could potentially become pandemic viruses. By getting a fairly comprehensive assessment of the breadth of neutralization or HI titers in the study population, one could gain a better prediction of what the efficacy would likely be for a real outbreak.

I noticed in your approach, from what you have shown today, you have one strain that was a heterologous target. But I'm wondering if you could share any other thoughts you would have on the approach to getting a more robust assessment of the diversity of responses or the breadth of responses.

DR. VAUGHN: There are a number of H5N1 viruses that can be used in laboratories that are not high-containment, as they have been reassorted. At GSK, we are looking at a number of different H5N1 virus antigens for

testing, both by HI and by neutralizing antibody. The example I gave is fairly extreme, in the sense that it's cross-clade, from clade 1 to clade 2. In experiments where we may look at clade 2.1 versus 2.2, there may be even more cross-reactivity in terms of antibody responses.

DR. MODLIN: Bob?

DR. DAUM: Just a quick clarification. In your slide entitled "Framework for Ethical Review," you mention that venipuncture is a common childhood experience. I would just like to get some information from you as to how common you think that is. In my experience, it's not very common, but I don't take care of healthy children in the community or well children in the community.

DR. VAUGHN: I don't have specific data for that. Using needles with children is fairly common, from the newborn nursery, with a heel stick or a finger stick or actual venipuncture, as we are doing here. I'm not sure the pain is that much different between those different approaches. Healthy children may have infrequent venipuncture. I don't have specific incidence or numbers for children in the U.S.

DR. DAUM: Might I suggest that it's a pretty rare childhood experience, and you might want to improve that language a little bit.

DR. VAUGHN: Well, my perspective is from a pediatrician, so is fairly common where I work. But I understand your point.

DR. MODLIN: Bruce?

DR. GELLIN: We spent most of yesterday talking about how to make better vaccines to provide better cross-protection for seasonal flu. Given what you have here with your adjuvant, can you comment about the company's plans to use an adjuvant for seasonal flu? I guess you have already told us that this is the body of information in children, but you might want to tell us some more about these plans if they are to introduce that product and what the development plans would be, particularly to bring a product like that down to younger children.

DR. VAUGHN: Yes, the company does have plans to utilize the ASO3 adjuvant with seasonal antigens. There is a trial under way now in 43,000 elderly to look at that age group, and also plans to look at children, where the adjuvant may provide benefit or children don't respond so well to antigen alone.

DR. MODLIN: Melinda?

DR. WHARTON: Given that there is a more robust body of experience with the ASO3 adjuvanted vaccines in adult, could you share with us a little more information about the safety experience, particularly addressing the issue of some autoimmune conditions, which I think is the thing that raises at least a theoretical concern?

DR. VAUGHN: GSK is sensitive to the issue, the concern about autoimmune with new adjuvant systems, such as this one. We have come to agreement with CBER on a list of

adverse events of special interest, many of which are presumed to be immune-mediated. Some are not, but many are. We are actively looking for those types of cases, not only in the Q-Pan program, but the D-Pan program and other programs that are using AS03, such as the efficacy study in the elderly that's under that I just mentioned.

Not surprisingly, we are finding some cases on this list. To date, they are not above expected background rates. We continue to monitor that.

I think on an earlier slide I mentioned that as part of our submission packet, we will be putting together an integrated summary of safety that will look across D-Pan and Q-Pan programs to assess that risk.

DR. MODLIN: Seth?

DR. HETHERINGTON: Just a little more information on the child who had the elevation in liver enzymes. It sounds it was a preexisting condition, but if the condition worsened post-vaccination, it would be considered a treatment-emergent adverse event. Can you comment on whether the liver function tests in that child increased subsequent to the immunization or were they stable?

DR. VAUGHN: I have limited information about this child. My understanding is that liver enzymes were, ALT around 200 or so on day 0. Since that time, they have gone as high as 300 to 500. They have gone lower. They have gone up and down over the last year. So it would be a

judgment call as to whether this is an exacerbation of a preexisting condition.

DR. HETHERINGTON: The fluctuations, then, were probably within some range that would keep it within the same grade, I would guess. It doesn't sound like it increased in grade. There are specific criteria for various grades of liver enzyme elevation.

DR. VAUGHN: Correct. And the child has remained asymptomatic.

DR. MODLIN: Dr. Debold?

DR. DEBOLD: I'm concerned about how we make decisions about vaccinating people who may be potentially at risk, particularly children. I'm assuming that if you had it to do over again, you probably wouldn't have enrolled this child in your trial. How should we go about deciding who should and shouldn't receive a vaccine with ASO3 in it?

DR. VAUGHN: If you are talking about the declaration of a pandemic, the decision of who should receive vaccines, and which vaccines, will be left to government authorities. If we are talking about 3 million to 7 million dying in the next pandemic, that's one decision; if we are talking about 350 million people dying in the next pandemic, that's another situation. There is a risk/benefit ratio to be considered there.

Were you going to ask about clinical trials prior to --

DR. DEBOLD: I think you said something about putting this in the seasonal flu vaccine as well. I'm assuming that this is going to eventually unroll here.

DR. VAUGHN: The question is how to decide the use of an adjuvant like AS03 for seasonal vaccines. I think that's probably a different question than what we are discussing today. But you look at data in adults first, as is being done, and start in a small number of children, if you move to children, and gradually increase that until there is satisfaction of regulatory authorities and advisory committees that the risk is acceptable from the vaccine to prevent a known quantified risk of seasonal influenza.

DR. MODLIN: Norm?

DR. BAYLOR: A comment was made, and I just wanted to make sure we address it. There was a comment made about any preclinical data that you had. I think Dr. Debold mentioned that. Do you want to comment on any of that?

DR. VAUGHN: Preclinical data in terms of efficacy or safety?

DR. BAYLOR: Primarily safety.

DR. VAUGHN: I won't be able to cite it completely for you. Small animal studies have been done and have been included in the IND submissions and will be updated for the BLA submission.

I think I may have missed the point of the question.

DR. BAYLOR: I just wanted to make sure -- Dr. Debold mentioned that. I interpreted her question as whether we could get some background on what the company has done preclinically, before going into these studies that you have gone into in humans.

DR. VAUGHN: There has been work done in small animals prior to going to clinical trials.

DR. MODLIN: Does someone want to respond from GSK?

PARTICIPANT: Yes. In the context of adjuvant systems, like we have done for the ASO for adjuvant, we are looking at the mode of action in the sense of the adjuvant does in the immune system. In light of rare events -- because that's what we are talking about here -- there is no recognized animal model that can help you with that. So basically the best way to progress on that is from these two studies and establish as best as is possible the mechanism of action of the adjuvant on the innate immune response, as well as the adaptive.

DR. MODLIN: Thank you. I basically heard you say that there is no recognized animal models to study human autoimmunity.

PARTICIPANT: Yes.

DR. MODLIN: We do need to move on. Dr. Vaughn, thank you very much. We have kept you up here longer than

we intended, but the information that you have presented, I think, has been extraordinarily valuable.

We will go on with the next manufacturer's presentation, which will be by Dr. Theodore Tsai from Novartis.

Agenda Item: Novartis Presentation

DR. TSAI: I'm Ted Tsai, representing Novartis Vaccines. Thank you for the opportunity to comment on the important public health and ethical question of pandemic influenza vaccine development for children.

We support such development under Subpart D 50.54. Although the avian H5N1 influenza virus currently is the focus of attention, because other avian and non-avian influenza viral subtypes also pose a pandemic threat, we believe the clinical research on vaccines against those subtypes also can be justified under a similar rationale.

Novartis is one of several companies that has conducted H5N1 vaccine trials both in adults and in children. To help inform the committee's discussion, I will review that clinical experience. But because the safety of adjuvants is part of the larger concern, I will first review our experience with our adjuvant, MF59, and our adjuvanted seasonal influenza vaccine, Flud.

We suggest that clinical trials of pandemic influenza vaccines in children can be supported under Subpart D 50.54, for a number of reasons. A pandemic, by definition, will affect the United States and large

segments of its population, including children. By common consent, everyone should have access to a pandemic vaccine. In times when vaccine distribution must be prioritized, as mentioned previously, the Department of Health and Human Services and the Department of Homeland Security have placed infants and toddlers at the top tier of recipients.

We believe that the justice principle applies equally to pre-pandemic vaccination. Indeed, a strategy of gradually priming the population over time could facilitate outreach to people who might have reduced access during an emergency.

As mentioned previously, children have borne a disproportionate share of the H5N1 cases since 1997, and along with adults under age 40, are also susceptible to H2N2 virus, which further strengthens the rationale for pediatric vaccine development.

Lastly, as mentioned previously, the approval of a smallpox pediatric vaccine trial under Subpart D 50.54 suggests that similar development of a pandemic vaccine for children also could be justified, since arguably the threat of a pandemic in the United States is no less than that for a domestic smallpox outbreak.

You have seen a reference to this document previously. This is the Department of Health and Human Services and Department of Homeland Security guidance on allocating pandemic vaccine. You can see in red that

health-care workers and other essential workers are placed in the top priority to receive pandemic vaccine under every pandemic scenario -- severe, moderate, and less severe. But within the general population, only pregnant women and infants and toddlers have received that prioritization.

I would like to describe our MF59 adjuvanted H5N1 vaccine, Aflunov. Aflunov is made by the same manufacturing process as our seasonal vaccine, Fluad, that also is adjuvanted with MF59, which has been licensed in Europe since 1997, with more than 40 million doses distributed to people over 65 years of age. As a monovalent vaccine, Aflunov contains .75 µg of the H5N1 hemagglutinin, along with MF59. Formulations with the clade 1 Vietnam and clade 2.2 Turkey/Turkey strain have been produced.

As mentioned earlier, Europe allows for approval of a mockup pandemic vaccine file, and such a vaccine, using the same manufacturing process and formulation as Aflunov, has been approved in Europe under the name of Focetria.

MF59 is an oil-in-water emulsion comprised of squalene, which is a naturally occurring oil and a precursor of human cholesterol synthesis. It also contains two surfactants in an aqueous buffer. The particles in this emulsion are stable for years.

There is an extensive clinical database and clinical experience for MF59 from the distribution of 40 million doses of Fludax since 1997 and actively collected clinical trial data from more than 25,000 recipients of MF59 adjuvanted vaccines. No safety signals have been observed from that experience.

The data from these clinical trials has been compiled, analyzed, and submitted to the FDA as a biologics master file. That master file comprises 94 clinical trials, many of them conducted under U.S. IND, and will compare the safety experience of recipients of Fludax and their non-adjuvanted vaccine counterparts, focusing on local and systemic reactogenicity and adverse events, including autoimmune disease, the new onset of chronic disease, cardiovascular events, hospitalizations for any cause, and deaths.

The more than 25,000 subjects in this database comprise principally adults, but it also includes 748 children, and the preponderance of all the subjects was enrolled at influenza vaccine trials.

Other sources of safety data in adults will be forthcoming from a large-scale observational study being conducted in Lombardy, Italy. This study links the vaccine and medical database and, in recipients of Fludax and non-adjuvanted seasonal vaccines, will compare influenza effectiveness outcomes, as well as vaccine-related, medically attended adverse events. We are seeking to

enroll 150,000 subjects. One hundred thousand have been enrolled. The final analysis is expected in 2010.

Lastly, we have a published analysis of the pharmacovigilance database for Fluad over an interval during which 27 million doses were distributed. In that analysis, no safety signals were detected for selected adverse events.

I would like to turn now to describe clinical data on Fluad, both in the indicated population of adults over 65 and experimental data in children.

Fluid is more locally reactogenic than unadjuvanted seasonal vaccines, but most of the adverse reactions are mild or moderate in severity and are transient. In a meta-analysis of 22 studies that traced Fluad and non-adjuvanted vaccine recipients over three consecutive seasons, there was an increase in reactogenicity with repeated vaccination.

On the other hand, MF59 also amplifies the immune response. In the same meta-analysis, Fluad and non-adjuvanted HI antibody responses for the three subtypes were compared and are shown here as a geometric mean ratio, with ratios above 1 indicating a higher Fluad response. I think you can see, for the three subtypes across all three years, the Fluad antibody responses were significantly higher.

MF59 not only raises the antibody response, but also broadens it to heterovariant or drifted strains,

influenza viral strains. I have shown here just the results for HI antibody responses to the H3N2 component of a vaccine in which the H3N2 component was a Wisconsin strain. The data are mapped against the CHMP criteria, the EU criteria described earlier for seasonal vaccine, with mean fold increase, seroconversion rate, and seroprotection, which is defined as proportion of subjects achieving HI titers of 40 or higher.

You can see that the Flud responses, in red, met those criteria, not only for the Wyoming strain contained in the vaccine, but also for three other H3N2 strains, including a California strain that circulated the following year and a Wisconsin strain that circulated two years later. Responses to the unadjuvanted vaccine were lower, shown in green.

So even though this vaccine was formulated to meet the criteria for the Wyoming strain, it would have met the CHMP criteria for H3N2 strains that did not circulate until one or even two years later.

Because the efficacy of TIV unadjuvanted seasonal vaccine in children is lower than that in healthy adults, we undertook a proof-of-concept study of Flud immunogenicity and safety in 6- to 35-month-old children in Finland. The children in this trial were randomized to receive half of the adult dose of Flud or a licensed split vaccine comparator. After the first 101 subjects were enrolled, an interim safety analysis was conducted. No

safety concerns emerged, and the trial resumed without interruption.

The subjects were invited to return after the initial season for revaccination the next year.

Fluad tended to be more reactogenic than the unadjuvanted split vaccine, but, as shown here for the first dose, only swelling at the injection site was significantly more common Fluad recipients compared to split-vaccine recipients, occurring in 12 percent of the Fluad recipients and 5 percent of the split-vaccine recipients. The pattern of reactogenicity after the second dose, after the revaccination dose, was similar.

The immune response data are shown here as seroprotection against the three subtypes. After the first dose, the antibody responses to Fluad were significantly higher for the H1N1 and H3N2 strains, and after the second dose, to the H1N1, with an even more pronounced difference for subtype B. Nearly 100 percent of the Fluad recipients achieved putatively protective HI antibody titers to the B antigen, compared to 30 percent of the split-vaccine recipients.

Of note, after just one dose, 90 percent of the Fluad recipients achieved putatively seroprotective antibody titers to the H3N2 subtype, meeting the CHMP criteria for young adults.

I show the same immune response data now as GMTs, geometric mean titers. In addition to the post-dose 1 and

post-dose 2 titers are shown the results of a follow-up bleeding six months later, ahead of the next season. The Fluvad responses were significantly higher at every time point for all three subtypes. The sustained elevated antibody titers, especially for influenza B, may be of significance, because, as we discussed yesterday, influenza B affects children disproportionately and also often occurs in springtime outbreaks.

Similar results were seen in another study that enrolled children up to 5 years of age. In this study Fluvad was compared to a U.S.-licensed comparator. The homologous antibody responses to the H3N2 and B antigens contained in the vaccine were significantly higher in the Fluvad recipients. The sera also were tested against strains that circulated the following year and that were mismatched. The Fluvad responses against all three of these heterologous antigens were significantly higher.

I would like to leave the data on seasonal vaccine and turn now to the MF59 adjuvanted H5N1 vaccine, Aflunov. I will describe the data first in adults. There is a growing database on Aflunov, approaching 10,000 subjects, including 334 children.

Here is the tolerability profile of Aflunov, shown in yellow, for young adults, on the left, and older adults, on the right. The Fluvad reaction rates are shown in brown for comparison, because Fluvad was used as a comparator vaccine in the trials.

Aflunov tended to be less reactogenic than Fluad, and most of the adverse reactions were mild or moderate in severity, with very few that were severe. You can perhaps see on the bottom of the bars an orange bar, which indicates the severe reactions.

The antibody response data are shown here -- again for young adults on the left and older adults on the right -- to the homologous clade 1 Vietnam antigen contained in the vaccine, in yellow. After two doses, 85 percent of the young adults and 79 percent of the older adults achieved putatively protective neutralizing antibody titers to the homologous clade 1 antigen. Six months later, their antibody titers had declined, but with a third dose, also containing the clade 1 antigen, antibody titers returned to protective levels in 94 to 97 percent of the young and older adults, respectively.

The sera also were tested against a heterologous clade 2.2 antigen, the Turkey/Turkey antigen. After the booster dose, 70 and 60 percent of the young adults and older adults, respectively, achieved putatively protective neutralizing antibody titers to the heterologous response. Please note that these subjects did not receive the Turkey antigen and were vaccinated only with the Vietnam antigen.

In another study, a smaller group of individuals' antibody responses were tested to a broader array of heterologous antigens, including a clade 2.1 Indonesia

strain, a different clade 2.2 strain, and a clade 2.3 strain. These were pseudotyped neutralization assays that are done because of safety concerns. It shows that the Vietnam-immunized vaccinees developed heterologous antibody responses to all there heterologous clades.

Expanding on this observation, and also looking at the persistence of immune memory, Novartis is fortunate to have a cohort of subjects who were vaccinated eight years ago with a clade 0 H5N3 adjuvanted vaccine. In 1997, after the Hong Kong outbreak, Chiron made an experimental H5N3 vaccine, because at that time there was no recombinant dilution H5N1C virus available. The H5N3 virus is considered to be antigenically related to an H5N1 clade 0 strain.

The primary neutralizing antibody responses to the adjuvanted H5N3 vaccine were significantly higher than to the unadjuvanted vaccine. Six to eight years later, the subjects were reconvened and immunized with Aflunov, the H5N1 vaccine. Within seven days of receipt of that H5N1 dose, all subjects made high levels of neutralizing antibody, not only to the H5N1 clade 1 strain, but also to viruses in clade 2.1, 2.2, and 2.3 that all had been associated with human H5N1 infections. Control subjects who had not been primed required two doses of vaccine to reach protective antibody levels, as you have seen previously.

This unique set of data suggests that in primed individuals, one booster dose of an adjuvanted vaccine can rapidly induce neutralizing antibodies to putatively protective levels to a broad array of related antigens after an interval of up to eight years after priming.

Proactive pre-pandemic vaccination could be facilitated if that priming could be achieved with just a single dose. In this study, subjects received one dose of the adjuvanted clade 1 vaccine, shown in yellow, and then a year later, a second dose containing a clade 2.2 antigen. Within a week after receipt of that second dose, both groups reached putatively protective neutralizing antibody levels to the respective antigens. Approximately 90 percent of subjects in both groups achieved those protective levels.

The second dose of this vaccine was given concomitantly with an unadjuvanted seasonal TIV without interference to the immune response to those seasonal antigens.

So these observations suggest that a single adjuvanted prime and boost dose with different but related antigens spaced a year apart could provide high antibody responses to both strains.

Finally, I would like to turn to available clinical data on children.

The pediatric H5N1 vaccine trial in children that I'll describe was approved by the national regulatory

authority, as well as the local IRB, without significant delay, in part because the clinical trial site previously had conducted the Fluvad pediatric trial, but also because the threat of H5N1 disease in Europe is tangible. H5N1 virus and other highly pathogenic avian influenza viruses have been isolated in wild and domestic birds in Europe, and human H5N1 cases have occurred in nearby Turkey. So participation in pandemic vaccine trials may have a benefit that is considered to be less than hypothetical.

The trial in Finland enrolled children 6 months to 17 years of age simultaneously, and all children who received Aflunov received the full 7.5- μ g dose. The children were in three age cohorts -- 6 to 35 months old, 3 to 8 years old, and 9 to 17 years old -- and were randomized three-to-one within these groups to receive Aflunov or Fluvad as the comparator, and Fluvad was given in the age-appropriate dose.

An independent data safety-monitoring board monitored the safety responses after the first 30 subjects were enrolled, after each of the doses. There were no safety concerns, and the trial was conducted without interruption.

I have only the data for the primary responses. The booster response data are pending.

This figure displays the local and systemic reactogenicity after the first dose, but the pattern is similar after the second dose. In general, rates of

adverse reactions after Fluad and Aflunov were similar. About 15 to 25 percent of infants and children had adverse events consisting of rhinitis, otitis, and cough. These were the most commonly reported adverse events. In adolescents, headache, pharyngitis, and dysmenorrhea occurred in about 5 percent of the subjects. There was no difference between the Fluad group and the Aflunov group in the incidence of these reactions.

The immunologic data are shown here, against the CHMP criteria, seroprotection rate, seroconversion rate, and geometric mean ratio. For each of the three age groups, you can see 97 percent, 97 percent, and 89 percent reached the CHMP criteria for seroconversion and seroprotection after two doses. For the third CHMP criterion, geometric mean ratio, that criterion was reached after the first dose, with a substantial increase of antibody rise after the second dose, to 129-fold, 117-fold, and 67-fold, respectively, reaching GMTs of 688, 585, and 344.

I have shown a large body of data that I will try to summarize, reflecting both the seasonal vaccine and the H5N1 vaccine experience, both in adults and in children. We have a substantial database of 25,000 subjects, with no safety signals detected thus far. The safety database for children is more limited, with 750 subjects exposed.

In seasonal vaccines, MF59 provides higher and broader responses, and in children, a single dose has provided seroprotective antibody levels to the H3N2 subtype.

I did not describe it, but there is a published study comparing in a head-to-head fashion an MF59 and alum adjuvanted H9N2 vaccine. The MF59 adjuvanted vaccine provided significantly higher antibody titers than the alum adjuvanted vaccine.

MF59 allows for antigen sparing, and two doses with the clade 1 Vietnam strain provided putatively protective antibodies to the homologous strain, as well as to strains in a number of other clades.

A strain-change study, in which a clade 2 antigen will be evaluated, is under way.

The durability of immunity was seen in a study in which recipients of a clade 0 adjuvanted vaccine were boosted six to eight years later, and rapidly, within seven days, produced neutralizing antibody responses at high levels, not only to the antigen in the booster vaccine, but also viruses in all clades that have been associated with human illness.

Finally, a single dose primed for homologous and heterologous responses upon receipt of heterologous booster one year later. This was achieved without interference in responses to the seasonal vaccine antigens.

Novartis also has in development an MDCK cell-derived H5N1 vaccine. A trial currently is ongoing in

young adults. Upon its completion, a pediatric plan will be developed.

In summary, children, including in the U.S., are at risk for infection with pandemic influenza viruses. There is a substantial clinical experience with MF59 adjuvanted vaccines that thus far has not indicated a safety signal, although data in children remain limited. MF59 adjuvanted H5N1 influenza vaccine in adults and in children has been immunogenic and well tolerated. Further clinical studies of pandemic influenza vaccines in U.S. children, we believe, can be justified as contributing to a better understanding of vaccine prevention against a serious problem affecting the health or welfare of children.

DR. MODLIN: Ted, thank you very much.

Dr. Tsai's presentation is open for discussion. Questions? Dr. Debold?

DR. DEBOLD: I just have a technical question. On slide 28, where you have the titers for the toddlers, children, and adolescents, on the far right, does that mean that in the adolescent group the average titer was 67 or is that the number of --

DR. TSAI: It's a bit confusing. This is geometric mean fold rise. With the second dose, there was a 67-fold rise in titer compared -- and so the geometric mean titer for that group, adolescents, was 344.

DR. DEBOLD: Okay. The standard that I keep seeing applied -- is it 40 that you would consider as seroconverted? Is that correct or not? So does that mean that, on average, adolescents' titer was 344?

DR. TSAI: That's correct.

DR. DEBOLD: Is that a lot more than what we need?

DR. TSAI: As was discussed earlier, we really don't know what levels of antibodies are protective against H5N1 infection. We have essentially extrapolated from the seasonal vaccine criteria, where a hemagglutination inhibition HI antibody titer 1 to 40 is considered to be protective. There are some clinical data and other data that would support that level, that immune correlate. But for H5N1 vaccine, there is very little data that I'm aware of that would inform identification of a threshold of protection.

DR. MODLIN: That's absolutely right. And, of course, these titers don't persist. In other words, these are titers that are obtained within a month after completing the last dose. Of course, there is going to be a decline in antibody titer, and so you have to factor that in as well when you are talking about seroprotection rates and correlates of protection.

Dr. Eickhoff?

DR. EICKHOFF: Ted, you mentioned a lot about absence of safety signals, but you didn't show us a whole

lot of safety data. Could you describe the surveillance protocol you used following receipt of one of the experimental vaccines? Was it active or passive surveillance? What did it take to generate a safety signal?

DR. TSAI: I don't know the details of those specific protocols, but, in general, in vaccine trials solicited adverse events are collected through diary cards. Depending on the age of the subject, those events can be different. For example, in the adolescents, you could ask about pain, whereas in infants the adverse event is tenderness. Those adverse events would have been collected for some interval -- I believe it would be seven days -- after each vaccination. Then other spontaneously occurring adverse events would be collected after each visit. Serious adverse events that would be reported spontaneously would be entered into the database as well.

So, in general, in vaccine trials you have solicited events that you deliberately try to collect and then all the spontaneously adverse events also are collected. Of course, among them, those that are defined as serious are analyzed separately.

DR. EICKHOFF: If I can pursue that one point further, what did it take to generate a safety signal? Some significant deviation from the appropriate control group?

DR. TSAI: The data monitoring board that oversaw the pediatric trials was given a rather broad definition

and ability to stop the trial, with any significant safety concern. There were no stopping rules, for example. Sometimes in a clinical trial you will specify a specific stopping rule. There were no stopping rules. But the overall database was examined, and the safety monitoring board would have had the liberty to interrupt the trial.

What I meant by safety signal, I was really referring, more so, to this database that has been collected, as well as to the pharmacovigilance database, which, admittedly, consists of spontaneously reported events. So the pharmacovigilance database, comprising reports that cover the interval where 27 million doses were distributed, found no increases in specific adverse events that were examined -- GBS, other neurologic diseases that potentially could be of an autoimmune nature, and others. I can't remember the specific events. But the incidence rates in that database did not exceed baseline expectations.

What we have with the data master file, however, is an ability to compare the safety experience of the MF59-exposed subjects with controls who received the same vaccine without the adjuvant. This provides for a much more powerful way of looking at the safety of the adjuvant itself.

We are in discussions with the FDA about this analysis, so I don't feel I can really comment at this time. But I can say, our own analysis is very reassuring.

DR. MODLIN: Jack?

DR. STAPLETON: I was interested in following that a bit also. In this clinical database, have you systematically looked at people who have received annual or repetitive doses of MF59? If not, have you systematically done that in your Fluad recipients in Europe?

DR. TSAI: There was a meta-analysis done. Two thousand subjects received Fluad, and there were 1,500 comparators in the first year, and then smaller numbers in subsequent years. The reactogenicity was followed after these three consecutive seasons. In fact, whereas in the first year there were significant differences in local reactogenicity -- pain, erythema, induration -- those differences actually disappeared after the second year and third year. So the difference in reactogenicity actually was reduced with a second dose and a third dose.

DR. STAPLETON: I'm interested in whether you saw any signals toward autoimmune diseases, in particular?

DR. TSAI: That wasn't -- the object of this study was to look at acute reactogenicity.

DR. MODLIN: Ted, the adjuvant produces extraordinarily high levels of antibody. Are the heterologous responses independent of the titer of antibody?

DR. TSAI: This is an interesting question. Do we see these heterologous antibodies because a rising tide lifts all boats? There is, in fact, a study -- I don't know the details of it, but it's a collaborative study that our group in Siena has with CBER scientists, in fact -- to look at that. There is a suggestion that we are actually seeing reactivity to other epitopes that are not seen with an unadjuvanted vaccine.

DR. MODLIN: It's obvious that you are priming for heterologous antigen, which I think is critically important. But I think that would also be an extraordinarily important issue to get at in terms of primary protection, particularly with one dose?

Roland?

DR. LEVANDOWSKI: There's another study that has been done looking at reimmunization many years later with two different H5N1 antigens. I don't think you mentioned that. John Trainor (phonetic) for NIH did some studies. In 1998, he did a study immunizing lab workers and others with the original Hong Kong 97 H5N1, the clade 0 vaccine, as Ted said. In that study he was actually looking at dose ranging, so he had all sorts of unusual combinations of very low doses to very high doses of the antigen. Some of those -- not all of those -- people were available eight years later and were immunized with Vietnam 1203 vaccine. The first vaccine was prepared by Protein Sciences. The Vietnam 1203 vaccine was prepared by

Sanofi. So they were totally different antigenically and also by the way they were manufactured.

The bottom line is that those individuals who had been immunized with Protein Sciences' vaccine eight years earlier also had extremely unusually, we would say, high antibody responses after a single dose of vaccine. Whereas the primary immunizations were getting geometric mean titers that, let's say, were about 30, those who were reimmunized years later were getting responses that were about 60.

It's not quite the same kind of study, but I think there is maybe a principle there that heterologous priming may occur even without addition of an adjuvant.

DR. MODLIN: Dr. Klimov?

DR. KLIMOV: Ted, just a technical question. I believe that in slides like this one for seasonal vaccine, the HI titers being measured using turkey red blood cells or chicken red blood cells, while for the H5 vaccines the titer is being tested probably with the horse red blood cells. This is correct?

DR. TSAI: Yes, I think that's correct. I have tried to show you micronute data in most cases. But, yes, in the HI cases it would have been horse erythrocytes.

DR. MODLIN: Dr. Gilbert?

DR. GILBERT: A comment. The data on the heterotopic responses is useful, but my comment is, I find it hard to interpret the results without seeing some map

relating the different target viruses to the vaccine virus. There might be some interesting work to do in statistical methods of looking at the antigen relationships and displaying those in some way, to set an interpretation framework.

DR. TSAI: That's an important question. I'm not involved in this research, but, as was mentioned yesterday, this antigen cartography allows for a very accessible way of understanding those antigenic relationships. Derek Smith at Cambridge University has made such a map for the H5N1 clades.

DR. MODLIN: Roland?

DR. LEVANDOWSKI: One more question, which I guess I should have asked the other speaker as well, because it would probably apply to both situations. A lot of the studies that are being described relate to comparing vaccine with and without the adjuvant. The benefit is as important as the risk, I think, in order to figure out what the risk/benefit ratio is. For those vaccines that have adjuvant in them, how difficult is it to do the standardization, to do the potency testing? Are there any special tricks that are necessary? When you are trying to compare one vaccine with another one -- they are not formulated exactly the same -- how much certainty do you have that you are actually comparing the same amount of antigen?

DR. TSAI: I'm not sure I'm the right person to answer that question, to be truthful. Maybe it's a rhetorical question.

DR. MODLIN: Maybe we can find somebody to answer you offline, if that's okay, Roland.

Bob Daum and then Dr. Klimov.

DR. DAUM: I don't know if you are the right person to ask this question, but you said it, so I'll ask you to clarify briefly. If you could put the last slide up for just a moment, which starts with "Summary." The first statement, that children in the U.S. -- I'm paraphrasing -- are at risk for infection, which I happen to agree is an underlying assumption as to why we are sitting here -- it strikes me that we should then approve research under 50.52. But you began your presentation by saying it is approvable under 50.54. I don't know if you appreciate the difference in bureaucratic intensity those two approaches involve. So you may not be the right person to ask. But they are huge. I wonder if you would comment on that statement versus 50.54.

DR. TSAI: I guess we were trying to take a more conservative approach, in the sense that there might be skeptics that H5N1 virus was not a direct threat, because we have had no isolations in the U.S.

But I personally do believe that there is certainly, as someone has said, a non-zero risk -- perhaps

it was you -- and that children may, in fact, be at higher risk, for reasons that Dr. Vaughn mentioned.

I think I may have forgotten to comment on a point in my slide. Children also may be at increased risk inherently because of the distribution of the cellular receptors for avian influenza viruses in the respiratory tract. They seem to have a greater expression of the sialic acid alpha-2,3-galactose receptors in the respiratory tract compared to adults. That could be an inherent biological risk factor for increased risk of avian influenza viral infections in children.

DR. KLIMOV: Just coming back to two remarks before. During the last big WHO discussion about the vaccine strain selection for the seasonal influenza, also the status of H5N1 vaccine development and vaccine strains was discussed. This is going to be published, if it's not published, very soon.

I have this data about the antigenic relationship between different clades. If necessary, I can show this very briefly, if this will help the discussion.

DR. MODLIN: Thank you. Dr. Joffe?

DR. JOFFE: I just wanted to make a comment that I could have raised with the previous speaker as well, and perhaps this will come up this afternoon. In interpreting the safety or adverse-event data, the comparisons between the adjuvanted vaccines and the non-adjuvanted vaccines or, for example, the H5N1 vaccine versus Fluad, I find it

difficult to interpret those comparisons, because, in a sense, the most interesting comparison, which I don't think we have, is the H5N1 adjuvanted vaccine versus a true saline placebo, with respect to the adverse events. What you find when there is an active control, as there is in, I think, most or all of the studies that have been presented, is that you get, potentially, an increased risk of adverse events in the control group, and then the question is, is the experimental vaccine in these comparisons elevated above that baseline? But that, in a sense, is an artificially inflated baseline for many of the comparisons.

So thinking about study designs going forward -- and, again, perhaps this will come up this afternoon -- I wonder if, from the point of view of adverse events, the favored study design might not be a true placebo as opposed to some sort of active placebo, which I think makes it very hard to interpret adverse-event data.

DR. MODLIN: That's a great point, and I think we can discuss that this afternoon. You can easily see arguments on either side of that. There's no question about that.

Other questions?

(No response)

If not, let's go on to the next speaker.

Ted, thank you very much for a very informative presentation.

The final speaker before lunch will be Dr. Richard Gorman, from NIH. Dr. Gorman is associate director for clinical research in the Division of Microbiology and Infectious Diseases at NIAID.

Agenda Item: NIH Presentation

DR. GORMAN: Good afternoon.

I'm well aware, after this discussion this morning, of the risks and benefits of being the last speaker before lunch, so I'll try to be brief.

The NIH experience with pediatric H5N1 trials consists of two trials which I hope to discuss in some detail.

The first trial is a randomized, double-blind, placebo-controlled Phase I/II study of the safety, reactogenicity, and immunogenicity of intramuscular inactivated H5N1 vaccine in healthy children aged 2 through 9 years of age. That is titled "DMID 04-077." In our nomenclature, "04" is the year in which the protocol is developed.

The second was an open-label study of intramuscular inactivated influenza vaccine in healthy children aged 2 to 10 years. That was a follow-on study to the 04-077 study, where all human subjects were offered the opportunity to receive the study vaccine.

The rest of this discussion will center on 04-077, with some comparisons to adult trials with similar vaccine products. All the products that we are going to be

discussing today are unadjuvanted and all the same product. The placebo that we used in ours is, in fact, a saline placebo.

The study design for 04-77 was a multicenter, with three participating centers. The centers were in the University of Maryland, St. Louis University, and UCLA, all in the United States. It was randomized five-to-one between the active agent and a placebo control, double blind. The population was healthy children. Children between the ages of 2 and 9 were enrolled in two strata, 2 to 5 and 6 to 9. This study was designed in 2004, and the standard seasonal influenza recommendations for pediatrics did not extend below age 2 at that particular time. That's why these age ranges were chosen.

The vaccine was an inactivated subunit of the influenza A/Vietnam. The dose, volume, and route: 45 µg of hemagglutinin in 0.5 mL given IM. The manufacturer was Sanofi Pasteur of Swiftwater, Pennsylvania.

The procedures for this study were: Two IM doses of the vaccine or placebo given one month apart. The third dose was offered at six months to vaccine recipients only, and it was optional. So all the participants got two vaccines and the people who got the study agent were offered the opportunity to get a third vaccine at that particular time.

Looking for reactogenicity, we had a memory aid for the first seven days, which was gone over by telephone

on day 7. There were clinic visits at regular intervals, both for the vaccines and the for the serologic draws during which reactogenicity and safety data was collected. There were telephone follow-ups from day 56 until month 12, looking for serious adverse events.

For immunogenicity, we did sera for both HI and MN, both before the vaccinations and one month after each dose.

For the immunogenicity data set, there were 125 children enrolled, 23 into the placebo arm and 102 into the vaccine. One hundred seventeen received two doses. There were 113 subjects with all sera available, 21 placebo and 92 vaccines.

The first question in terms of safety and reactogenicity: Was the dropout rate different in the placebo and the vaccine group? The answer was no. The ratio of five-to-one maintained in the dropouts as well.

The booster dose at six months: Fifty-eight vaccine recipients were boosted, and 55 of those had sera at 28 days.

The gender of this population was 54 percent boys, 46 girls; 89 percent Caucasians. The median age in the study was 6 years of age. The cohort between 2 and 5 had 61 subjects; the cohort between 6 and 9 years of age had 52 subjects.

There were two serious adverse events. Both were deemed unrelated. One was a case of rotavirus diarrhea 13

days after second vaccination. There were other family members ill, and a rotavirus ELISA test from the stool was positive.

The second case was a case of rat bite fever. It was 55 days after the second vaccination. It was purportedly due to Julie, who was the newly purchased pet rat. The subject was hospitalized for persistent high fever and received IV antibiotics. Other immunological tests looking for other diseases all turned out to be negative, except for rat bite.

Continuing on with the safety drill-down, there were 141 adverse events: 61 percent were mild, 12 were deemed related; 37 were moderate, two deemed related; and 2 percent, or three total events, were related as severe. All of those were considered to be unrelated. Of the three events in the severe group, two were in the placebo control and one was in the study group, the active vaccine group. The one that was in the study group was an intercurrent non-influenza-like illness that also shows up in our reactogenicity data.

Drilling down further to the reactogenicity of this antigen, there were no fevers over 103. There was one mild and two moderate after dose 1, two moderate after dose 2, and one moderate after dose 3. There were no severe reports of injection-site pain. The redness was mostly mild, up to 20 mm.

I'm going to show the reactogenicity data in two different ways, first this way, in a graphic form, and then in a more visual form, for those of you who are graphic learners versus those of you who are visual learners.

In this particular slide, we see the reactogenicity data after dose 1 for all of the reactogenicity events that exceeded 5 percent. If you look at the slide, we have the vaccine participants versus the placebo. In the white are the total number of any severity of reports during the first seven days and in the red are any that are moderate or severe.

Not surprisingly, injection-site pain differs between the two groups, and perhaps decreased activity. But other than that, the groups look remarkably similar.

After dose 2, the results look remarkably the same – again, decreased activity, again the gap narrowing, injection-site pain continuing to show a difference between the vaccine and the placebo.

After dose 3, there were no placebos, because this was only given to the vaccine recipients, and these were their responses.

For the visual learners, we look at it this way after dose 1. On the y-axis you see the percent of all who complained. Inside the graphs you can see severe, moderate, and mild, in three different color representations.

After dose 2.

Then after dose 3.

As one of the considerations this group is going to have over the rest of this session is the risk of this group versus other groups, I thought it might be useful to show the parallel nature of this versus some of our adult data.

This is a slide comparing the pediatric and adult reactogenicity of children and adults who receive the same antigen in the same dose, again unadjuvanted. You can see that the panels look very similar, except for elevated temperature, which appears on the pediatric side but not on the adult side. But when you use 45 μg in both pediatrics and adults, the reactogenicity post-vaccination looks remarkably the same.

When you go up to 90 μg , the dose approved for adults, you will notice that the charts now look slightly different, with adults complaining of a lot more pain, which is consistent with the data that we have received over the years that the more antigen you put into a vaccine, the more pain there is at the local injection site. But if you look at the systemic signs of elevated temperature and body aches, they remain the same in both groups as well.

Talking a little bit about the efficacy or the immunogenicity of this particular vaccine, we would like to look at the microneutralization results. In the blue boxes you will see the placebo results. There is no change in microneutralization; in the brown boxes, ages 2 to 5, fourfold increases after doses 1, 2, and 3; and in the

yellow boxes, the microneutralization increase after doses 1, 2, and 3, for ages 6 to 9.

The hemagglutination inhibition results: Again, you see the same sort of results, with the placebo having no increase; ages 2 to 5, after 1, 2, and 3, going from 6 to 53; and the age group 6 to 9 going from 41 to 64 percent.

Again, because this group is going to be looking at and talking about the risks for pediatrics, as well as the benefits for these types of studies, we wanted to show you the results of this particular study, 04-077, versus two studies that we have done in adults, one with healthy adults and one with stable-health-condition elderly, all receiving the same doses.

In this particular time, post-vaccination 1, there was 7 percent increase in the peds, 21 percent increase in healthy adults, and 7 percent in the elderly; post-vaccination 2, 38, 33, and 23; and post-vaccination 3, 58, 38, and 17.

This is looking at the same dose, looking at the dose that is presently approved in adults. We have gone from the 45 µg that we have used in pediatric subjects to the 90 µg that we have used in adults. You can see that the initial response after dose 1 is better for the adults, with pediatric subjects only receiving a 7 percent increase, while adults receive 23 or 25. But by vaccination 3, the resulting increase in hemagglutinin inhibition looks pretty similar across the three groups.

In summary, two IM doses of 45 µg of unadjuvanted inactivated H5N1 vaccine in children is well tolerated, leads to immune response comparable to adult responses, and there is a slightly better response in 6- to 9-year-olds compared to 2- to 5-year-olds.

Thank you. I'm available for questions.

DR. MODLIN: Terrific. Dr. Gorman, thank you very much.

Are there questions for Dr. Gorman? Yes, Dr. Klimov?

DR. KLIMOV: Again, this technical question. The slide on page 20, HAI data, is this with use of horse red blood cells or turkey red blood cells?

DR. GORMAN: I can't answer that question because I wasn't involved in the assay work, but I can provide that data for you before the end of the meeting.

DR. MODLIN: Ann says it's horse. Dr. Joffe?

DR. JOFFE: The various IRBs that approved this protocol -- do you happen to know what subparts they were approved under?

DR. GORMAN: The communication from IRBs goes to the principal investigators. The essential documents that we collect inside of NIH are that they were approved. I perhaps could go back and get that information. I do not know that off the top of my head.

DR. JOFFE: Just to follow up, was this approved by NIH IRB or was it all local IRBs?

DR. GORMAN: This was all local IRBs.

DR. DAUM: But isn't it true that if the IRBs approved, it wasn't 50.54?

DR. GORMAN: That is correct. They were approved at the local level.

DR. JACKSON: Just a point of clarification. On these slides, does this mean that the measure of a post-vaccination titer greater than 1-to-40 is the same as the definition of a fourfold rise? The footnote indicates post-vaccination titer greater than 1-to-40, but the title is "Fourfold Rise."

DR. GORMAN: They had to meet both criteria. They had to have a fourfold rise and the final titer had to be greater than 1-to-40.

DR. MODLIN: But the data in the boxes are fourfold rise?

DR. GORMAN: That is correct.

DR. MODLIN: Other questions?

(No response)

If not, Dr. Gorman, thank you very much. We certainly appreciate the presentation.

We have a lot of work to do this afternoon in a relatively short period of time, so I'm going to ask all the committee members to return on time, ready to begin the discussion. We will start at 1:15 on the dot.

(Whereupon, at 12:15 p.m., the meeting was recessed for lunch.)

AFTERNOON SESSION

DR. MODLIN: Good afternoon. I would like to reopen the meeting.

I know that a number of committee members and others have flights this afternoon. Even though the agenda says that we are going to 4:00, we have a target finishing time of 3:00. I'm hoping that we will be able to conclude by then. However, we do have a lot of work to do, so I'm going to ask people to try to recognize that reality.

The next item on the agenda is the open public hearing. I understand we have at least one individual who has signed up for the public hearing. Before starting that, I need to read the following statement.

Both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision making. To ensure such transparency at the open public hearing session of the advisory committee meeting, FDA believes that it is important to understand the context of an individual's presentation. For this reason, FDA encourages you, the open public hearing speaker, at the beginning of your written or your oral statement to advise the committee of any financial relationship that you may have with the sponsor, its product, and, if known, its direct competitors. For example, this financial information may include the sponsor's payment for your travel, lodging, or

other expenses in connection with your attendance at this meeting.

Likewise, FDA encourages you, at the beginning of your statement, to advise the committee if you do not have any such financial relationships.

If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

I understand that we have at least one speaker who has signed up, Dr. Mary Kathryn Reeves-Hoche. Dr. Reeves-Hoche, would you like to begin?

Agenda Item: Open Public Hearing

DR. REEVES-HOCHE: Thank you, Dr. Modlin, committee members.

I'm Dr. Mary Kate Reeves-Hoche. I work for Sanofi Pasteur, where I am the director of the pandemic influenza program in the R&D stage. So that's my financial disclosure.

Sanofi Pasteur is very proud to have partnered with HHS and the DMID of NIH in licensing the first H5N1 influenza vaccine for the United States in April of 2007. Since that time, our company has moved on to test lower dosages of antigen with different adjuvants -- namely, aluminum salts and our proprietary oil-and-water emulsion adjuvant. Our vaccine has been tested in a stepwise fashion, first unadjuvanted, as already presented by Dr.

Gorman from the NIH, and then with the aluminum adjuvants, and now we are testing with our novel adjuvant.

We have had great success in our adult program using this novel adjuvant and have achieved a very high immune response at the lowest dosages of H5N1 antigen reported to date. A vaccine containing only 1.9 µg of antigen generated a high level of seroprotective immune response in over 70 percent of the participants in a clinical trial. In the same clinical trial, vaccine containing 3.75 µg of antigen generated a high level of seroprotective immune response in over 80 percent of the participants. Again, these were adults.

Based on this experience, we are advancing our clinical program into the elderly and into pediatric populations. In fact, as already mentioned at this meeting, we have an ongoing pediatric trial in Thailand using H5N1 plus the aluminum adjuvant.

We recognize the vital importance of pediatric populations and the importance of protecting that population, but we also recognize that they are considered a special population, with additional regulatory safeguards. Sanofi Pasteur believes that by working with committees such as this, as well as working with the FDA, we can safely evaluate H5N1 vaccines in pediatric populations.

We would like to acknowledge the support that we have received from the U.S. government in our

collaborations with the NIH, as well as our collaboration with other manufacturers.

Thank you.

DR. MODLIN: Thank you, Dr. Reeves-Hoche.

Let me ask if any of the committee members have questions for you.

(No response)

If not, thank you very much.

Is there anyone else who wishes to make a statement in this portion of the meeting? Yes?

DR. CHU: Thank you. My name is Susan Chu. I'm a physician by training. Right now I'm contributing editor of Flu Wiki, which is an online Web site on pandemic flu. I'm also a cofounder and president of Ready Moms Alliance, a nonprofit, grassroots effort for promoting pandemic preparedness.

I don't have any connection with any of the manufacturers in the room or any in industry in general.

I want to, first of all, thank the committee and everyone who has worked so hard on it. Coming from where I'm coming from, I'm fully cognizant of the threat of a pandemic, and the threat to our children. Right now, as we speak, in San Diego, Ready Moms Alliance is presenting in an exhibit the issue of the risk to children of H5N1 because of the high mortality. As far as I'm concerned, I think that we ought to go as quickly as we can, in any way we can, to promote any studies that would lead to a

pandemic vaccine being available, if and when the pandemic breaks out.

Having said all that, when I listen to the subtext that's going on, I think the biggest concern is the safety, specifically with regard to adjuvants. Instead of going to the details, I want to take a 30,000-foot view of that and ask questions.

When you put an adjuvant and an antigen into a child, the reason why you would put that would be because the antigen is a little bit too weak to produce the immune response that you want. But at the same time, when you put that in a child, the child's body also has a whole lot of auto-antigens going around that are weak, that are not causing problems, that are being suppressed into producing disease because of tolerance.

I'm not a research scientist on that aspect. I don't know whether, particularly with broad-acting adjuvants that act across different vaccines, their effect on the antigen that you are putting in, the vaccine antigen, would also have the same effect on the auto-antigens in the child's body.

There is a second level to that question, when we look at adverse-event reporting. If you give a child a vaccine, how do you know he or she is protected? We don't know until you expose the child to the disease. But if you don't have that, what you do is, you monitor for antibodies. But in a case of auto-antigens and similar

kinds of induced response, what we are doing right now that I'm observing is waiting for much further downstream, when they actually have symptoms, for them to report back.

What I'm looking at is, there is a disconnect. The parallel of the antibody testing for vaccine antigen does not exist -- we don't have the ability yet to test accurately whether the child is having those kinds of responses. Before we have that ability, I would say, on the one hand, it's good to have vaccines as quickly as possible, but on the other hand, I would say, go slow, because we don't know what we are looking at.

The other part of the story is, I would suggest that it is very important to tell the public where the areas of uncertainty are, what it is that you don't know, what it is that you can't work on. My experience of talking to the public online for three years is that the vast majority will understand complex decisions, where you can't have the perfect solution. You have to tell them and explain to them, and they can get it.

Thank you.

DR. MODLIN: Thank you, Dr. Chu. Perhaps during the next hour or so, we can address a couple of the issues that you raised.

Are there any other members that wish to speak during this portion of the meeting?

(No response)

If not, we will go on to the committee discussion and recommendations to the agency.

Agenda Item: Committee Discussion and Recommendations

I would like to lead off by reminding us -- we have heard a terrific, very thorough, careful explanation of the regulatory and the ethical frameworks for our discussion today -- I want to remind the committee that our purpose here is really not to discuss the ethical issues per se. Rather, we are constituted as a technical advisory committee. I think the agency would prefer that we devote most of our attention to the technical issues, overlaid over the ethical framework that we discussed earlier this morning. That's really our purpose here, and I'm going to try to keep the discussion focused in that way, if at all possible.

The questions that we have presented to us, I think, help in that respect. It may very well be that the best way to begin our discussion would be focusing on the first question here: Please discuss whether clinical studies in one more pediatric age groups should be conducted using inactivated pandemic influenza vaccine candidate as part of pandemic preparedness.

Of course, in my opinion, one of the issues at the very heart of this question is the issue that Dr. Daum raised earlier, which is, just what is the risk of pandemic influenza in a population of U.S. children?

I don't mean to say that this is where we have to start, but I think it might be a reasonable place to start. So I'm going to open this up for committee discussion.

Bob, do you want to start off with any further comments around that issue? I think you made your point clear -- oh, one other thing I do need to say is that we will not be voting on any of these issues. It's really the discussion part that is, I think, the critically important part of the meeting this afternoon.

Bob?

DR. DAUM: I can just reiterate in one sentence. I think that at some point an influenza pandemic is going to occur. There is no information about what form it will take, when it will come, or what virus will be the perpetrator of it. But I believe very strongly that when it does happen, children will be involved in helping to spread the virus and be involved in the epidemic, if that's the right word to use. Therefore, in thinking of preparedness and plans to get ready, I believe very strongly that children need to be included in understanding their immune responses to vaccines and preventive measures that we as a scientific community want to develop.

I guess I don't understand a reason to exclude them. I don't see a rationale for directly extrapolating from adults information on what to do with dosing and regimens in children.

Beyond that, I think I have made my point clear, and I'll stop talking. But I'm a strong proponent that children should be included in influenza preparedness, by understanding their responses to the vaccines we heard about today.

DR. MODLIN: Dr. Jackson?

DR. JACKSON: I agree. I think it could help us to consider that the question could read "should continue to be conducted," since studies of pandemic vaccines have already been conducted in children in both the U.S. and elsewhere. The critical issue seems to me to be the degree to which you can extrapolate from older age groups to pediatric age groups. I don't think you probably can for these vaccines, and so we need pediatric-specific data in order to develop vaccines and schedules that will be most likely to protect the pediatric population.

DR. MODLIN: Ted?

DR. EICKHOFF: I totally subscribe to Bob Daum's point of view, as expanded on by Lisa Jackson. I think there's no other reason we are here today. We are worried about children. History teaches us over and over again that children are at risk if there is going to be a pandemic. We can argue about whether it's going to be H5N1 or something else, but that's really a nonproductive argument at this point.

DR. MODLIN: Pablo, do you feel any differently?

DR. SANCHEZ: No. I absolutely agree. I think as pediatricians, we always complain that we have to treat our infants and children based on adult data. We have to look at it in pediatrics.

DR. MODLIN: Dr. Gilbert?

DR. GILBERT: I agree with everything that has been said. Nothing more to add.

DR. MODLIN: Pam?

DR. MCINNES: I completely support it. I think, in addition, we have to have a learning curve as the data are derived, in terms of understanding how we can perhaps start collapsing age populations, et cetera, and not assume that everybody will march down exactly the same path. But we have to learn from the data as they accumulate. I really think they need to be extremely robust in order to build a body of safety and immunogenicity data that we have a lot of confidence in.

I don't know if you are going to get in the next question, but I have strong feelings about how rigorous the informed-consent process should be.

DR. MODLIN: We can come back to that. José?

DR. ROMERO: I concur with everything that has been said. I think this is a unique opportunity for us to really, as pediatricians, serve as the voice of our population of medical interest. I think this is an opportunity to really move this vaccine development forward.

It's intriguing. There are lots of avenues that we can talk about.

DR. MODLIN: Seth?

DR. HETHERINGTON: I agree completely. I think a question that might be raised -- maybe not today, but in the future -- is, how much information is going to be needed to feel comfortable with the use in children? Just looking at some of the numbers that we have, we have the DMID study of 125 kids and the Novartis study of 472-plus kids.

Just to put it a little bit in context, if you have 300 patients' worth of data over a period of time that you think is adequate and there are no serious adverse events, then you have a 90 percent certainty that any serious adverse event is going to be less common than 1 percent. If you look at the other side of the coin, the risk that a pandemic would present, 10 to 40 percent infectivity among kids with a 60 percent mortality, it doesn't take a whole lot of calculation to figure out that you are well into the benefit-plus column of doing this.

I think the key point, perhaps, is that we will have data on kids down to 6 months of age. A question that should be raised is, do you need to go even younger than that? I think some of the epidemiology we saw earlier is that under 6 months is a very at-risk population.

The usual limitation we have on seasonal flu vaccine, going down to 6 months, I think assumes that under

6 months you are protected by maternal antibody to some degree. But I'm not certain that we have any information that says the same will be true with an H5N1 virus. So we should give some serious consideration to pushing that age limit down to as low as possible, to cover the most susceptible patients.

DR. MODLIN: That's an excellent point.

Vicky?

DR. DEBOLD: I think this question as stated is sort of -- the trials are already happening, so it's not a matter of saying you do or don't agree with them.

I think I'm less enthusiastic than what I have heard so far. I'm not convinced that the information that I have about specific risks to American children, at this particular point in time, is compelling enough to go into large-scale trials with children, absent doing some of the preliminary early things that, for me as a member of the public, I feel are missing. It seems like much of the discussion today has centered around a tension between the need for production efficiency versus the potential for creating unintended and potentially unnecessary autoimmune problems in some susceptible individuals.

I think we have to be very careful, because all of this is being played out now in an arena of challenged, I think, public trust as it relates to vaccination. It's very important that whatever is done here is done correctly. If there is no pandemic and if it doesn't ever

come, but yet we have many sick children, there will be an extremely high cost to having made that choice.

DR. MODLIN: Norm?

DR. FOST: There are two separate questions on the screen. One is whether or not a pandemic is likely -- or implicit questions. I don't have any expertise on that.

But the next question is, if a pandemic occurred in the U.S., would it be better to just vaccinate children based on adult data or would it be better to do studies? I think it's clear that we can't wait until the pandemic starts. I think we have seen evidence that it's too late at that point to start studying it. Therefore, if it's going to be studied, it has to be studied before the pandemic comes.

I think as a general matter it's preferable to study things systematically than to just give kids things off-label and hope for the best and see what happens. I think we have too much history of things gone haywire that way.

So it all hinges on the likelihood of a pandemic. If that likelihood was zero or close to zero, then doing studies would be exposing children to risk with no benefit, because nothing would ever come to help them. If we thought it was an extremely high likelihood of a pandemic, then it seems to me self-evident that we need to do these studies now, before it comes.

So it seems to me the whole thing hinges on the likelihood of a pandemic, which is outside my area of expertise. But as an informed lay person reading the literature, it seems to me likely enough and that the risks of doing these studies are low enough that it's appropriate to do these studies now, before the pandemic comes.

DR. MODLIN: Maybe I could just address a point there, since I'm next in line. I was talking with Melinda Wharton and others during the break this morning. This is, in some respects, déjà vu all over again, with respect to discussions that we had at the CDC and the ACIP around recommendations for smallpox vaccine about six or seven years ago.

I was told this morning that testing the smallpox vaccine in children does not create a precedent for this discussion that we are having today. But I do want to point out that, as Bob and others have said, the issue of whether a pandemic will occur or not is really less of an issue. It's not a matter of if it will occur; it's a matter of when. That's the lesson that history has told us.

With the smallpox discussion, it really was a theoretical discussion. Nobody really knew whether there was any risk whatsoever, which made the decision making that much more difficult.

But I would like to point out that if we had an outbreak of smallpox, as bad as it would be, an outbreak of smallpox would be far easier to control and probably cause

far less morbidity and mortality than, say, would an outbreak of a new strain of influenza virus, without a doubt. We know that we can control an outbreak of smallpox much quicker and much easier than we can an influenza pandemic. So in some respects, that's where the comparison breaks down. I think pandemic influenza is likely to be a more serious disease than smallpox may be.

I personally would agree. I think it's essential to do these studies, because children probably would be harmed in such a case if we didn't have the information that would come from clinical trials, if we needed to apply a vaccine suddenly that we didn't know how to use.

I'll leave it at that. I'll pass things on to Dr. Joffe.

DR. JOFFE: I'm inclined to agree with the majority sentiment that has been expressed so far that one ought to go ahead with these studies. But there's an issue that I think requires further discussion. Part of coming to that conclusion, I think, is concluding that one can't validly extrapolate from adult data to pediatric data. That has sort of been asserted in the discussion thus far, but it hasn't really been discussed in any detail. I don't claim any expertise to discuss it. It's certainly not my area of expertise. But I think it is worth a discussion of why it is that we can't validly extrapolate from adult to pediatric data. I didn't see in the presentations before any great differences between

adult immunogenicity or safety outcomes compared with the pediatric outcomes that were presented.

I'm not trying to argue that one can't. I just think it's an important issue that needs discussion, and I would like to hear more about it.

The other thing that I just want to raise briefly comes to the point of whether there ought to be studies in children younger than 6 months. Thinking about the pre-pandemic situation, it seems to me not necessary -- I'm thinking ahead, if a recommendation might come out for pre-pandemic population-wide vaccination, based on studies that have been done -- it seems to me unlikely that one would require pre-pandemic vaccination in very young infants, because there would be very little cost in this elective setting to saying the recommendation could be to wait until they are 6 months old and then vaccinate them. So I don't know that one needs data in the pre-pandemic setting on vaccinating kids that are younger than some minimum age, whether it's 6 months or something.

On the other hand, there might be a case to be made for studying those vaccines in young infants, thinking ahead to the pandemic setting, as opposed to the pre-pandemic setting.

DR. MODLIN: Bruce?

DR. GELLIN: In some ways, being in this position is easier because a lot has been said or harder, to try to identify some other issues.

We spend a lot of time talking about preparedness. It's interesting that the question is framed in the context of pandemic preparedness. Bill Robb, who recently retired from the Department after 45 years, often defined preparedness as what you want in place the day before the pandemic. I think that's both in terms of what stuff you want, what you want people to know, and what other knowledge you have.

I think, in that context, we clearly know that just-in-time clinical studies are not going to give us the data we need, so getting ahead of that curve and knowing what we need to know ahead of time is really very important.

The other piece of this is that a number of people highlighted in their presentations the work that HHS, with Homeland Security -- and, frankly, across government -- did to try to look at the pandemic vaccine-allocation scheme. It's worth highlighting that the scheme that was presented is for severe pandemic. There are slight differences in prioritization if the pandemic is deemed not to be quite as severe.

Nevertheless, when we took this issue to the public and tried to take the pulse of the public about what they felt, it was clear that an important value to the public was protecting children. Protecting children is what this discussion is about, which is why I want to reinforce what Pamela said. We really need to know this information. We have to do it methodically, cautiously,

and comprehensively, because we want to make sure that we are doing what the public really sees as an important value here.

Not to confuse us with a separate discussion -- it's the one that Steven just raised -- we do have a stockpile of vaccine. There was some mention made of that. We continue to accrue vaccine into that stockpile. The current plan is, when a pandemic is imminent, it would be used.

But there is a separate discussion that we are having, that the World Health Organization is having, and that essentially every country with a stockpile is having on whether or not you would use it before.

Again, if you start thinking about the size of a stockpile that could be more broad than select populations, such as occupational groups, this is information that we are going to need to know. But again, as we said, it just needs to be obtained in a cautious and comprehensive way.

DR. MODLIN: Thank you. Roland?

DR. LEVANDOWSKI: I would like to give an example that is a rationale for thinking that what happens in children may not be the same as what happens in adults. Although there may be instances where everybody responds just the same -- H5 might be one of those where everybody who is immunologically naïve looks like they respond to the vaccine. Perhaps there are subtle

differences in local reactions and so on, but in terms of immunogenicity they look pretty similar.

But if you go to some other example -- I don't know whether you consider it a pandemic or not -- when H1 reappeared, it was very obvious that there differences in immune responses between those who were old enough to have been exposed to H1 previously and those who were not. It didn't separate out into children versus adults, but it separated out into people who were younger than about 25 years of age and older. Those who were younger required two doses of vaccine to get a tiny immune response, as compared to those who were older, who only needed one dose to get a very robust immune response.

We know very little about the other influenza A subtypes. I don't think we should forget that those are as important for pandemic preparedness as H5 and the other things that we have been discussing this morning.

I think that would be something to keep in mind, that we really don't know exactly what to predict. It might turn out that a lot of them are like H5, where everybody is naïve and the same. But there could be some unexpected cross-reactivities that would in some way impact on how we try to approach things. And we couldn't know that without doing the studies.

In addition to that point, as Dr. McInnes raised yesterday about the opportunity to optimize, I don't think we have fully optimized use of inactivated influenza

vaccine in pediatric populations, in the first place. I think there is a lot that we don't know about the dose that would be optimal. Again, it goes back to having not a lot of supply when these decisions were made.

The 6-month cutoff was somewhat arbitrary. Studies were done that were set up to cut off at age 6 months. That's what information was available; that's what FDA could support in the licenses that were administered. If the studies had started at 2 months, I suppose, we would have a vaccine that we would consider for 2 months.

There are other questions that relate to whether younger children really respond effectively to inactivated vaccine. There is that kind of discussion. I'm not negating that at all.

Again, we have an opportunity to try to do something more.

The last point is that, whether it's pandemic or interpandemic, influenza doesn't really make that distinction. The viruses are out there circulating somewhere. Although we are compartmentalizing them, they really overlap a lot. A lot of the information that comes out of the studies that are done for pandemic can help to inform how the interpandemic vaccines are used. We may be able to improve utility of vaccines for pediatric populations.

In the other direction, too, if those optimization studies were done, in some sense, for the current seasonal vaccines, that could help in developing safer and more effective vaccines for use in children.

DR. MODLIN: Thanks, Roland. Jack?

DR. STAPLETON: I would like to reiterate what you said, John. This is different, I think, than smallpox. There is H5N1 disease in the world. The question is, will it hit North America and will it be the pandemic? Given that there will be a pandemic -- or there will be a severe epidemic, at least, as it drifts -- if it does turn out to be H5N1, this will provide direct benefit to the children, which is something that we often don't have the option to talk about in all these discussions. If it isn't H5N1, it will at least provide dosing of novel hemagglutinin types that will provide us some information that may help with whatever does evolve.

The second issue that we will, I'm sure, discuss a lot more is that the poor immunogenicity of H5N1 raises the issue that you probably are going to need an adjuvant. That's new for flu in the States, at least. I think that's something that we will have a lot more discussion about. But it complicates the discussion.

DR. MODLIN: Frank?

DR. DESTEFANO: I agree with everyone that the possibility of a pandemic is not negligible, so I'm in favor of proceeding with such studies. I would encourage

studies that would focus, as some of the ones we have heard about, on either vaccines or strategies that will have as broad a protection as possible. I don't think we can predict when the pandemic will occur. We are not sure it will be H5N1. So strategies that will increase protection, whether through additional antigens or adjuvants or whatever, I would promote.

I would like to focus most of my comments on the safety concerns, the theoretical ones that have been raised about autoimmune disease, particularly from the newer adjuvants. I would say it's not likely that we will get good information on that until after licensure. Even 25,000 adults that have been enrolled in some of these trials are probably not adequate to really evaluate these pretty rare conditions.

I support Dr. Chu's suggestion of investigating the possibility of subclinical markers. I think maybe someone ought to give some thought to that, if there are available markers that could be included in some of these clinical studies.

Also I think it's worth looking at some of the data we have, particularly on the ASO adjuvant that has been used in 20 million adults in Europe. I don't know if they have been published, but I would like to see an analysis of what the pharmacovigilance data has shown, I would think -- the MF59 or the ASO, whichever one is in the Flud. I think that's the one that has been used in Europe.

Anyway, if there are 20 million doses that have been used, I think the pharmacovigilance data on that could be revealing. We have seen that, although it's voluntary reporting, the experience in the U.S. is that serious autoimmune diseases, like GBS, can be detected through a voluntary reporting pharmacovigilance system.

In children, I think we ought to take a closer look at influenza vaccine in general, if that has any associated risks, along the lines of neurologic or autoimmune diseases. There have been case reports of things like ADEM, acute disseminated encephalomyelitis. The early studies have been done of the TIV vaccine from VAERS. They were done early on. There may not have been enough doses of the vaccine to really evaluate those. I think, now that we have had more years of use in children -- I don't know what the dosage may have been, probably in the millions now -- it could be worth revisiting the VAERS data and VSD data to look at these issues.

DR. MODLIN: Thanks, Frank. Melinda?

DR. WHARTON: I do support the continued performance of pediatric studies looking at these influenza vaccines. Just building on some of the comments of my colleagues around the table, I do think we have a chance to do it in a thoughtful and careful way -- I'm sure we will get into this subsequently in the conversation -- to take things one step at a time and in a thoughtful, reflective

way, and particularly as we are thinking studies using adjuvants about which we don't have as much experience, to have that process be a staged one that is really based on careful consideration of the basic science and preclinical data, the prior experience in adults, and use of other vaccines -- in a very thoughtful, reflective way, before we take those pediatric studies.

DR. MODLIN: Thank you, everyone.

I think we have identified a number of questions that we need to come back to -- I think particularly Dr. Jost's question about when data in adults is adequate, which we can do. But I think probably our time is best served if we go on with the discussion.

If the recommendation is that studies should be conducted, please discuss your recommendations regarding -- and the first sub-bullet here is, which pediatric subpopulations should be considered.

I did hear Seth raising the possibility of infants under 6 months of age. The obvious reason is that in a pandemic situation the absence of passive acquired immunity could be very important. The disease could be quite different in that population than we currently see with seasonal influenza.

Another subpopulation to consider would be infants and children who have higher than normal risk from influenza of hospitalization, particularly children with chronic cardiac and pulmonary disease, children with

chronic neurologic conditions, and these sorts of underlying health problems that we know put them at higher risk from influenza morbidity.

There are probably other populations that I can't think of right now. I think those might be important ones.

Rather than go around, why don't we just open up this question for discussion about which pediatric subpopulations would be important. Seth?

DR. HETHERINGTON: Could I just ask a question first? That is, how do people think of use of a pandemic vaccine -- in other words, if a case has been identified or a cluster has been identified, do people think in terms of just wholesale immunization of the U.S. population, or are we talking about geographically targeting an area first, including first responders? That may affect how you approach some of these other questions.

DR. MODLIN: Let's let Bruce Gellin address that. He's the man of the hour here.

We heard some of that from the manufacturers today, about priorities for pandemic --

DR. HETHERINGTON: Priority in terms of populations, but how about prioritization in terms of geographical location? How do you perceive this?

DR. GELLIN: Maybe some of the folks in the flu group have a better descriptor of this. Often, when you look at seasonal influenza, it's not like the weather map, where you watch something start in the West and work its

way East. The description is more like popcorn. Once it's around, it will show up in various places. The assumption is that while there would be an effort, probably led by the World Health Organization to try -- I think containment may be optimistic -- to try to slow things down at the source, were that not to happen, then it's just assumed that it will spread across a continent and across the world.

Therefore, efforts to try to hold this off in some area I don't think are part of the current thinking, other than initially trying to slow something down in its tracks.

Is that your question?

DR. HETHERINGTON: Yes. Attached to that, then, is, what's enough of a signal to trigger wholesale immunization of the population? Is it a single case? Is it multiple cases? If so, how many? What triggers immunizing everybody?

DR. GELLIN: The World Health Organization has a series of phases. We are currently in what is referred to as a pandemic alert, which is Phase 3. The graduation of the stages will go when there is evidence of efficient human-to-human spread. It's a combination of the epidemiology and perhaps supplemented by some of the virological changes. Essentially, the lead would be the World Health Organization to declare a change in the phase of the pandemic alert, where we are now, and that then

triggers a whole cascade of things, both in the United States and other countries.

DR. MODLIN: José, you have a comment?

DR. ROMERO: In my previous life I worked as one of the physicians in the Public Health Department in Omaha. One of the things that's very important to keep in mind is the logistics of immunizing large numbers of individuals. This can't be done in a day, two days. It has to be done over time. There will be an early warning, but, as you said, there will be these indicators of when to start immunizing. You don't want to be trying to catch up. You want to be ahead of the curve on that one.

DR. GELLIN: Just to highlight, if the product requires two doses, then you have to build in not only the logistics time, but the time for the immune system to catch up to what it's supposed to be doing.

DR. MODLIN: Yet another reason to study it ahead of time.

Let's get back to this question, though. Are there subpopulations that should be studied, at least on a pre-pandemic basis? How about kids under 6 months of age? Pablo, do you want to address that?

DR. SANCHEZ: I definitely think that it should be. I think one of the problems currently is the fact that we don't immunize those infants. There is some data to suggest that they may respond -- unpublished. But I think that relying on the fact that they may have maternal

antibody is saying that that pregnant woman was immunized late in the pregnancy with the same vaccine. We just can't assume that in a pandemic setting. So I really think that it should be taken gradually to the young infants, less than 6 months of age.

DR. MODLIN: So you would support studies in younger infants.

DR. SANCHEZ: Yes.

DR. MODLIN: Jack?

DR. STAPLETON: I think that's definitely an age group where you can argue that you can't use adult data to extrapolate.

DR. MODLIN: And who may benefit the most, when you think about it, from what you learn, for a couple of different reasons.

DR. GELLIN: And also to recognize what's available from the medicine chest, antivirals are not currently available for children that age either.

This does raise the issue about pregnancy. It's not a subpopulation of children, but -- it has come up a couple of times here -- there is the question about maternal antibody and what impact it may have. I think the kinetics of that are study-able -- obviously, not the impact of vaccinating pregnant women, but it will highlight that, while this meeting is all about children, when you look at that list, pregnant women are also at the top of

the list. In past pandemics, they have probably fared the worst.

DR. MODLIN: Good points. José?

DR. ROMERO: A comment about antivirals. There is a study going on right now looking at dosing kinetics in kids down to 2 months of age. So that data will be coming forward.

Another group, I think, John, from a global perspective, is HIV-infected children. That is a group worldwide that we need to look, because they, too, will be at very high risk for this.

DR. MODLIN: Lisa?

DR. JACKSON: Getting back to your earlier question about subgroups as chronic cardiovascular disease, pulmonary disease, it seems to me that it would be reasonable to extrapolate from healthy children to children with diseases that are not immunocompromising. You would not necessarily have to conduct studies among those subpopulations. That would be one area where you could, I think, have more generalizable information.

DR. MODLIN: That's a good point. The only issue might be tolerability to the vaccine, as opposed to immunogenicity, in that group. A safety issue could be somewhat different in that group -- maybe, maybe not. That's the only caveat there.

Seth?

DR. HETHERINGTON: The other usual subgroups that come up here are children with nephritic syndrome or antibody-deficiency syndromes. It might be interesting to know if the use of adjuvants helps those groups any compared to the naked vaccine.

DR. MODLIN: Children with nephrosis are immunocompromised only when they have nephrosis. It's because they are losing antibody, which is typical only for a week or two during their exacerbations.

We could probably get into lots of different subpopulations here. But what I was trying to raise earlier were the general ones that we recognize for children that are truly at increased risk for influenza.

Pam?

DR. MCINNES: I guess my issue is a little more pedestrian. In terms of looking at those 3- to 5-year-olds and 6- to 9-year-olds, it seems that a natural group is 2 to 9, if we are stepping down from adult data. I didn't see a need to stratify within those based on data.

Then I guess the next group that comes to mind is the 6- to 24-month-olds, because we do immunize children from 6 to 24 months old right now. You would actually have some comparative data that you could look at. Then the question of the 2- to 6-month-olds -- of course, the question, then, on concomitant administration of other vaccines and safety in that regard. I think there would

just be a whole host of parameters that might play out in that.

But from an age-group perspective, I can see kind of a methodical way of stepping down.

DR. MODLIN: Good points. Norm?

DR. FOST: John, just going back to your general comment that the children we would want to study are the ones at highest risk, and coming back to a point I made earlier, that would be children in the most endemic areas. Ideally, the earliest trials should be in the children who have the most to gain from it, which is not in the United States.

DR. MODLIN: That's an excellent point. It certainly raises some of the ethical issues as well. I think probably we should take a minute or two to discuss that. I think the point was made that even though we haven't seen any disease in the Western Hemisphere, the number of cases that have been seen in the tropics and the Eastern Hemisphere number in the hundreds, which makes it still an extraordinarily rare disease in these groups. You can identify, obviously, high-risk factors as largely children who have been exposed to avian influenza through exposure to avian flocks, domestic avian flocks for the most part.

I'm thinking out loud here. It raises major challenges, I think, in study design, in trying to study a vaccine in those groups, and whether or not that is

technically feasible or possible to do, in order to address the ethical issue of considering them to be at high risk.

I'm not being very articulate here --

DR. FOST: What design problems did you have in mind? There are logistical problems and political problems, but --

DR. MODLIN: I was including those. Also I think there is this issue of whether they are truly at higher risk, which I think is probably open to interpretation. Of course, that also would depend upon the stage at which you are in terms of -- but here, in 2009, I don't think a child in Western Europe is at any higher risk than a child in the U.S. A child in Turkey probably is, albeit the risk there is still extraordinarily low.

DR. FOST: But, as you said, children who are raised in communities where flocks of chickens are in their backyards -- I don't know how many children you would need for these trials -- that would seem to be the ethically ideal population in terms of risk/benefit ratio.

DR. MODLIN: How do others feel? Bruce?

DR. GELLIN: I guess I'm not sure what this group is going to do with that kind of discussion, other than to highlight what I mentioned before, that there is an ongoing discussion at the World Health Organization, which is acquiring a stockpile, on how that stockpile might be used as well. I would think that this question is going to be the same. If you are going to be thinking about the use of

a vaccine in a population, then what are the considerations before you get there?

I don't know how much we need to weigh into that. I think it's an important thing to highlight, and maybe to transmit that to the World Health Organization, what our deliberations as we have considered this one.

But I'm not sure what we are going to do with that information. The manufacturers may already have information on some of the studies that are going on in a whole range of these populations. I took "risk" as meaning to be risk of complications from influenza, not risk of exposure in this.

DR. MODLIN: Both. I think that's what Norm is getting at, and then the ethical issue of whether or not we shouldn't be conducting it in someone who is at slightly higher risk of exposure.

But I think the point to be made is that the risk of exposure of children in this country is extraordinarily low, but it may not be a whole lot different than the risk of a child in Turkey.

DR. FOST: You don't want to study an HIV vaccine in Idaho. You want to study it in a population where the risk of HIV is extremely high. It seems to me it's the same principle -- unless there are compelling reasons not to.

DR. MODLIN: We'll be careful. We won't go there. That could raise a whole other -- Bob?

DR. DAUM: It is interesting to sit and parse out which children play with birds and maybe generate a little cohort of children at slightly higher risk. But they may be different. They have more preexisting antibody, for example. They may have a different kind of exposure. I think it begets the question: What do we want to know, and when do we want to know it?

My argument would be that there is going to be a pandemic of flu. I have no idea whether it will be this coming season or beyond my lifetime. But I'm in favor of ideas to get our population ready for such a pandemic, and "ready" includes antivirals, perhaps, and includes vaccines, almost certainly. And I would like to know how those vaccines perform in healthy children. By "healthy" in this context, particularly for Dr. Nelson's benefit, I'll say people who aren't necessarily exposed to chickens and aren't necessarily at high risk.

So I have no objection to doing studies in children in countries where they run around with chickens and where there are cases. That's fine. Those are going on, it sounds like. But I also think we want to know about people that are currently not in those high risks.

That's the argument that I have been trying to advance, and I'm going to continue to stand there.

DR. MODLIN: You are saying that's the public health imperative.

DR. DAUM: I think it is.

DR. MODLIN: Any other comments about this? Vicky?

DR. DEBOLD: I disagree with enrolling sick kids, little kids, into these trials at this point. I don't think we know enough yet about developmental immunotoxicology as it relates to the adjuvants. I think the story that we heard this morning about the kid who had elevated liver enzymes and developed subsequent issues -- many of the kids now are immune-activated. They are allergic. They have food allergies. We know that the two adjuvants that we talked about today really turn on the immune system. So what happens when you really turn it on?

I think there's a lot of basic science that needs to be done before we go there.

DR. MODLIN: Thank you. Roland?

DR. LEVANDOWSKI: One more comment about risk. We have been very focused on the highly pathogenic avian influenza viruses, because they are very scary. They do kill people when they infect them. We haven't been as focused on the possibility that a pandemic of influenza might start from some other source --

DR. MODLIN: H2 or something.

DR. LEVANDOWSKI: It could be H5. We have non-highly pathogenic avian influenza viruses across the United States. There has been H5 in the Southwestern United States and H7 in Virginia. These things exist in the wild avian populations here. There's nothing that really tells

us that there couldn't be a reassorting event of some sort that happens in some child or person who lives on the farm or goes hunting or gets exposed to something while they are involved in nature in some way.

So I think, in terms of the risk, it's not just risk because there's something scary happening in Asia or Europe, and it doesn't seem to be the same scary thing happening in the United States. The fact is that there is the possibility that another event could originate a pandemic here, which we would still need to deal with in a similar way.

DR. MODLIN: Jack?

DR. STAPLETON: I would like to respond a bit. I wouldn't advocate that we use adjuvants to test the idea of autoimmunity. But the opposite of that is the possibility that, actually, by immunizing with adjuvants, you may have a beneficial effect on asthma and autoimmune diseases. I would say that one thing that should be built into these vaccine studies, where you have a definite outcome measure, is longer-term follow-up to look at both harm and good from these vaccinations.

DR. MODLIN: I'll let you and Vicky debate the hygiene hypothesis. That's exactly where you're going here, which I fully understand.

Norm, in terms of pediatric subpopulations, what I'm hearing is that there is some enthusiasm for testing novel vaccine antigens in kids younger than 6 months of age,

and probably less enthusiasm for children that we have put in other high-risk categories. Dr. Jackson's point was that unless they are immunocompromised, the expectation is that their ability to respond to the vaccine would be very similar to that of healthy kids. The only question might be whether or not there's a different adverse-event profile. I think that would be something that would need to be taken into account on a case-by-case basis.

DR. BAYLOR: Also we want to touch upon, is there anywhere in that pediatric population that you can extrapolate, instead of doing studies across the board in, say, zero to 18 years of age. We used the word "subpopulation" to look at that as well, where there would be some age groups that you wouldn't necessarily have to study, where you would be able to extrapolate to others. I'm assuming -- maybe I'm incorrectly assuming -- that that would be the case.

DR. MODLIN: You are talking about extrapolating adult data down to a certain --

DR. BAYLOR: No, even within the pediatric age group. If I did a study in adults, should I do studies in 16- to 18-year-olds? Should I do studies in 15-year-olds? If I do studies -- what you have already said you would like to see are studies in children below 6 months of age. If I did studies in below-6-months-of-age, perhaps there are age groups above that I may not do studies is -- just getting into those subpopulations.

Pam, you made comments about the 2- to 6-month age group and the complications with that because of the concomitant immunization schedules in that timeframe. You mentioned the 2- to 9-year-olds.

I guess what I'm getting at is, it's not necessarily to study the whole range of the pediatric population. There are areas where you could extrapolate within there. I just want to get some confirmation of that.

DR. MODLIN: I'll let others weigh in here, but I would think that certainly kids that postpubertal, teenagers, could probably be studied with adults, or adult data could easily be extrapolated to them.

As everybody knows, the reason that we study the age range that we do now with seasonal vaccines is that up to at least 5 or 6 years of age, kids don't respond as well to inactivated vaccines, at least to one dose, probably because they don't have the immunologic memory to do so. Once you get beyond 5 or 6, up closer to 8 or 9 years of age, you are more likely to see responses that we observe in adults.

That's with seasonal vaccine. With a novel vaccine, obviously, all bets are off, and we have to consider them immunologically naïve.

Jack?

DR. STAPLETON: I think Pam's 2-to-9 group -- if those data are very similar to adult data, then I would think you could extrapolate in both directions.

DR. MODLIN: That's where I was going. Dr. Joffe?

DR. JOFFE: I just want to say something again that I said when we were going around. I haven't yet heard a compelling rationale for studying, at least at this point, the younger-than-6-month-olds, if you are thinking use in the pre-pandemic setting. I think the first question, the policy question, is, what do you envision the pre-pandemic population-based recommendations to be? What would be the minimum age at which you would start to vaccinate infants in the pre-pandemic setting? Then you want to be sure to study it up until that age limit at which the policy recommendations would kick in.

I think the issue of what you need to know in the younger-than-6-month-olds if you are thinking about use in the pandemic setting, not the pre-pandemic setting, is different. There you might well say, whatever the facts are, the truth is, in the event of a pandemic, we are going to vaccinate everybody, and we are going to assume that we can extrapolate from, say, 6 to 12 months down to the younger infants, and maybe you don't need those studies.

I think that's a different discussion. But I think in terms of what the lower age limit is, the first question is, what are the pre-pandemic policy recommendations going to be? Then let's make sure we have the information to guide administration of the vaccine within the scope of those policy recommendations.

I realize we can't answer that, because the policy recommendations aren't in place. But that to me is the thought process.

DR. MODLIN: I guess I would turn that around, by saying that I would guess that whatever science we have or data we generate will drive the policy, rather than the other way around. That would be my guess. I think that's what we are talking about here. I would hope so.

Norm, anything else about subpopulations that is important? Have we had an adequate go at that?

The next question is the adult safety and immunogenicity data needed to support proceeding to pediatric studies. We have been talking around that.

In your deliberations, please consider both the use of novel adjuvants and also whether other viral subtypes, other than H5N1, should be studied.

Again, we have had some discussion on both of those. Why don't we specifically focus on the adjuvant issue here?

It sounds to me like we have heard an awful lot this morning about the importance of adjuvants with novel antigens, in both adults and children. It seems very hard to think that we are going to get away from not needing adjuvants, particularly since they are so antigen-sparing.

Let me ask how others feel about that. Any disagreements?

DR. JACKSON: No. It seems clear that there is substantial benefit to adjuvants, and we would want to give the most beneficial vaccine. You, of course, want to start studies in adults and move down, which has been the way it has been proceeding so far. It's hard to imagine that new studies would proceed any differently.

DR. MODLIN: Any disagreements? Ted?

DR. EICKHOFF: That's fine and good, and I would support beginning with adults and moving down. But in the event of a threatened pandemic, you may not have the luxury of being able to derive adult data before you move into younger age groups. So it depends on the assessment of how much time you have at your disposal. But again, in the event of a threatened pandemic, you may not have that time.

DR. MODLIN: Jack?

DR. STAPLETON: I think, as Lisa said earlier, we are at that stage. We actually have quite a bit of data in adults. So I wonder whether we really need that much more adult data at this point to recommend going forward. From what I have seen from this morning's presentations, I would think that we have quite a bit of data in children and adults. So moving ahead makes sense.

DR. MODLIN: Christine, why don't you put question number 2 up there, if you wouldn't mind?

Any other discussion about viral subtypes? Roland and others have raised some important issues.

Dr. Gilbert?

DR. GILBERT: I would like to expand on a topic I brought up earlier, which is the use of a standardized panel of influenza isolates. I mostly work on HIV vaccines, and in that field, it developed by different sponsors using their own strains to evaluate their vaccines, and on the basis of antibody levels or T-cell levels to those strains, they would advance the candidates up the pipeline in clinical trials. So the field recognized that there was an urgent need to get several panels of standardized HIV isolates that would be shared, so that all vaccines can be compared using the same panel, so we can then interpret, in a head-to-head way, what the antibody or the T-cell data mean.

That might be something that needs to be part of the testing process here, to try to move toward a standardized panel that, in some sense, is representative of the antigenic types that putatively could lead to a pandemic.

DR. MODLIN: We had a lot of discussion about testing of panels yesterday with seasonal influenza. Obviously, WHO and CDC are tracking the ongoing changes with H5N1 and certainly have a panel of viruses. I would guess, Dr. Klimov, that that panel is, for the most part, available to FDA and to vaccine manufacturers as well? It's probably changing --

DR. GILBERT: In the HIV field, our goal is to update the panel periodically, regional panels, as well as subtype-specific panels.

DR. KLIMOV: The panels, every six months, come together for seasonal influenza, and they update the situation with the H5N1 at this time. We also have regular conference calls with HHS on the development and evaluation of influenza H5N1s in particular and the recent status of the vaccine candidates' preparedness.

There are several groups, including several groups in the United States -- one of them is CDC; another one is St. Jude Children's Hospital -- that are preparing vaccine candidates from different clades and sub-clades of influenza H5N1 viruses. There is a discussion on the evaluation of recent H5N1 viruses, their antigenic profiles, antigenic differences between different clades, sub-clades, and what would be suggested as next potential vaccine candidates.

Right now vaccine strains, essentially, from clade 1 are available. Vaccine from sub-clades 2.1, which is Indonesian virus, is available. There are vaccine strains, a couple of them, from sub-clades 2.3.4, which are viruses which are mostly in China. There are vaccine candidates from the sub-clades 2.2. There is work done on the clade 7. There was only a single case in China in 2003, but there was a human case of clade 7. So there is work on clade 7 vaccine development. Within, for example, sub-

clade 2.2., which is the most widely geographically distributed sub-clade, there are several candidates, including, most recently, viruses from Egypt which seem to be antigenically and genetically more advanced.

So this work is regular and it's under watch by HHS, by WHO, and by different groups.

DR. MODLIN: Thank you. Roland?

DR. LEVANDOWSKI: Along those same lines, I think part of the question about standardization, if I understood what you were saying, is that you want to be able to compare results from different laboratories. That's actually not very possible, with either hemagglutination inhibition or microneutralization, for flu. There has been a lot of work done to try to understand that. There is no international standard for the different flu strains. Although the strain itself may be the same, there are variations that may occur as it's passaged in the laboratory to prepare it to be used in these different types of assays. The assays themselves have some different features to them, the way that they are handled.

The point is, there have been studies that have done comparing different laboratories. This information has been published for seasonal-type vaccine, and there is a study that is about to be published for H5 as well. They say the same thing. Even though each of the laboratories has what would be considered a validated assay -- internally, everything is consistent and it's reproducible

and reliable -- when you try to compare the results from the different laboratories, there may be fourfold, eightfold, even higher differences between the absolute titers. You see that in the information that is provided for the committee here for strain selection every year. Those panels that are used by the different labs to test the sera -- you see that the absolute titers are different.

Within that context, though, what you will see is that some labs tend to be higher, some labs tend to be lower, and if you tried to rank the different sera that you were looking at, you would see that they generally are ranked pretty much the same. But the absolute titers are not that easily comparable. If you were trying to look at, to use the term of art, seroprotection between different vaccines and different studies, it's very difficult to do that sort of extrapolation.

DR. GILBERT: I don't want this to go on too long, but how, then, might you recommend that policymakers decide on recommendations for choosing one sponsor's vaccine versus another sponsor's vaccine, if you can't interpret their data in a comparable way?

DR. LEVANDOWSKI: I'm not sure I can answer that question directly. I think what needs to be done for the vaccines is to demonstrate that they are immunogenic and safe. I don't think we actually know, particularly for H5, what the true protection level is for any antibody. The

correlation there hasn't been done yet, so we don't really have enough information to say. But I think we can generally say is that more is more in terms of antibody against influenza. The higher the titers, the more likely there is to be resistance to infection, less likelihood of complications and deaths. It's a matter of trying to increase that as much as possible, and therefore, a lot of the discussion about the adjuvants that we are having now.

DR. MODLIN: That's a perfect segue into this last question: Please discuss what pediatric safety and immunogenicity data you would consider adequate to support licensure of inactivated pandemic influenza vaccine candidates for use in one or more pediatric populations. Again, we are asked to consider both the use of adjuvants and other viral subtypes, other than H5N1.

Bruce?

DR. GELLIN: This is a licensed pandemic vaccine?

DR. MODLIN: That would support licensure for a vaccine to be used in one or more pediatric populations.

DR. GELLIN: At what point in time? At the pandemic or tomorrow?

DR. BAYLOR: We're not talking about, necessarily, tomorrow. If the pandemic has been declared, we would like to use this vaccine to immunize our population. What type of data would you recommend for that?

DR. GELLIN: A pandemic vaccine in the setting of an imminent pandemic, not a pre-pandemic vaccine.

DR. BAYLOR: Not pre-pandemic, correct.

DR. MODLIN: I would guess that it would be very similar to the discussion we had two years ago on the Sanofi H5 vaccine for adults. We're pretty much in an analogous situation for children, are we not?

What would be an adequate safety database? Jack?

DR. STAPLETON: John, it might help the group if you kind of went through the discussions and summarize them from the Sanofi licensure.

DR. MODLIN: I'm sorry?

DR. STAPLETON: It might be helpful if you wanted to summarize the discussions from the Sanofi licensure -- the idea that this vaccine would be used at the start of an imminent pandemic as a way to provide some immunologic memory. Or am I oversimplifying?

DR. MODLIN: Be my guest.

DR. STAPLETON: The way I remember that discussion -- in my typical oversimplification way of thinking -- is that having a stockpile of a licensed vaccine that, if a pandemic was imminent, would be distributed in a systematic way to those at highest risk and on down, not with the hope that the clade 1 vaccine would protect against the pandemic strain well, but that it would provide some immunologic memory, it might provide some protection, and it might be a boost phenomenon when the pandemic vaccine came around -- maybe I'm oversimplifying.

DR. MODLIN: So not necessarily to protect against disease, but to protect against significant morbidity and mortality. That was the whole idea.

Really, the question is, what do we consider an adequate safety database? I think Roland the point, which we all would agree to, that we really are in completely uncharted territory when it comes to deciding an adequate level of antibody we could use as a surrogate for protection. We just don't know. We would never know until we had the opportunity to actually employ a vaccine. So we have to rely on other data to make judgments about what we consider to be adequate immunogenicity.

How about the safety database? Let's focus on the safety database here. In other words, what sorts of studies would you consider to be adequate to support licensure in the pediatric age group? Pamela?

DR. MCINNES: Several hundred in each age group. I don't think I would stretch to thousands as being necessary, but a robust hundreds number would be -- in terms of numbers.

May I retreat one step to the previous -- if the principles of what you want to see in the immune response would be possible to articulate. Even though we don't know an absolute number we want somebody's titer, we would hope that there is indication of children being primed, that there is a booster response, that we have some understanding of the kinetics of the response, duration of

the response; if you could think about vaccine as essentially a la challenge with virus, that they responded. I think we would want to see indications of kinetics that might indicative of a favorable response.

DR. MODLIN: And you would want to test enough kids that you would have confidence that the results were generalizable. I'm not sure that we can get a whole lot more precise than that.

DR. MCINNES: Right.

DR. MODLIN: Bob?

DR. DAUM: I think Pam is right. I like to think of the safety issues as the ones that are retrievable with the hundreds-of-thousands kind of sample size and then the ones that require the millions and tens of millions to retrieve that are really quite rare. I don't think it's possible, particularly in this instance, to think about the large-scale kind of detection, with 10 million or 1 million people. I think we have to rule out common and relatively rare -- I like the way the speaker from the Netherlands spoke this morning about that -- rule out the relatively rare side effects, with a sample size of about the size that Pam is saying, and then remember that if we need to use this vaccine on a wholesale scale, we have a disease with 60 percent mortality, or maybe more, and that finding a very rare side effect might be less important than rolling it out to large numbers of people.

So as best as I can sit here and guide you, not knowing what's going to happen when, I would say that something that passes the hundreds-to-thousands test for safety and immunogenicity and any other data we can bring to bear on it ought to be licensed and prepared -- or considered a candidate for preparation. Let's put it that way.

DR. MODLIN: Whether it includes an adjuvant or not.

DR. DAUM: Whether it includes an adjuvant or not.

DR. MODLIN: Seth?

DR. HETHERINGTON: We are throwing numbers out. Let's, again, put them in context. If your definition of a rare event is 1 in 1,000 or less, you need a database of 3,000 patients to rule it out. If you are willing to accept a rate of 1 percent, you need 300 patients' worth of data.

So, really, what it comes down to is, in the setting of a pandemic, what do you think your infection rate is going to be? What do you think your case fatality rate is going to be? Balance that against your effect of the vaccine, which includes your seroconversion rate. What do you think the reduction in mortality is going to be or reduction in disease burden, however you want to quantitate these things? Then it's a simple calculation after that. That tells you what your expected benefit is going

to be. And then how much risk are you willing to take on in order to gain that benefit?

Unfortunately, there are going to be some assumptions that you have to make along the way. But unless you make those assumptions, there's no way to calculate the risk/benefit ratio.

You just have to keep that in mind as you start putting numbers out there. Do you want a database of several hundred versus a few thousand? What does it really mean? You just have to think about how much of a risk you are willing to take.

I would bet that if we had, tomorrow, a severe pandemic and you started having lots of kids in the hospital and you started seeing deaths, you would probably take the data you have today and say, let's start immunizing kids.

So you have to think of it in terms of the range of possible outcomes that you are going to get with your pandemic and then, again, what you are willing to take on as a risk.

DR. MODLIN: Good points. Lisa?

DR. JACKSON: I would also agree with Pamela in arguing for the several hundred. Also keep in mind that we would want to have the ability to evaluate the possibility of adverse events that are not uncommon and also that are expected to occur relatively proximate to vaccine administration. Some of these more hypothetical concerns

regarding autoimmunity and so forth -- I don't know that it would be possible to study those, even with much larger sample sizes. For one thing, you would need to follow people for a long time. For another, you would have to have a randomized placebo group of fair size, which, especially in the younger populations, could be a real issue, because then you start getting away from the possibility of direct benefit to your study participants.

So I think we ought to be as constrained as possible.

DR. MODLIN: Thank you. Dr. Nelson?

DR. NELSON: I would just like to ask a follow-up question to Seth's balancing of the calculations, which strikes me as quite useful. Given that the studies to support the pandemic indication would be done in the absence of an existing pandemic, would you use the calculations you went through to argue that you could use a smaller study for licensure, given that the risk/benefit in the actual use condition would be different than if you were going for, say, a pre-pandemic indication? You would limit the size of the study which is being done in the absence of a pandemic, understanding that the information you would need would be set against a much larger risk and disease burden in the event of a pandemic?

DR. HETHERINGTON: Right. And that's why I brought up earlier on the question of under what circumstance you anticipate using this vaccine. I think we

have been talking mostly about a pandemic situation, not a pre-pandemic situation, in which case you would be vaccinating many to have benefit for, potentially, very few or benefit that is pushed off well into the future. You have to discount what that benefit is relative to your immediate risks around the time of immunization.

That's an even more difficult calculation that I can't even begin to conceive. But I think if you make some assumptions about what would happen in a true pandemic situation, you might be able to come up with an answer that, in fact, would lead you to accept a smaller database -- certainly a smaller database than 3,000.

DR. MODLIN: Bruce?

DR. GELLIN: Seth is right. The math is easy; it's the assumptions that are the hard part, and which assumptions you are going to use. It's worth remembering that part of the pandemic preparedness exercise was the development of what we refer to as the Pandemic Severity Index. It recognizes that pandemics can roll out in different ways, and depending on the severity, you might do different things.

As a country, we have sort of taken the most severe pandemic and tried to use that as the bar. Whether that's the equivalent of this, that may help to drive which assumptions you use. But the other things that we do are based on the most severe pandemic and then can back off

from that, with the theory that it's better to plan for the worst rather than hope for the best.

I think the other piece that this question -- we are discussing this question as it's asked, but we can't forget the second part of this. Once a vaccine is licensed, it doesn't mean we stop looking. A large part of the discussion around the Sanofi vaccine initially was the systems in place that would be able to evaluate the things that you wouldn't be able to pick up pre-licensure.

So I think we can't forget that. That's not what the question is about, but it's not as though once this thing is licensed, that's the last time we consider it.

DR. MODLIN: Good points. Dr. Joffe?

DR. JOFFE: We have been talking mainly about the safety database in terms of numbers needed to have a reasonable sort of precision around safety estimates. But I think an issue that Dr. Jackson raised is, how long of a safety follow-up do you need on these kids? I think it's an important issue to be reckoned with. Are we talking about safety follow-up on the order of months? Do we need one-year follow-up? Do we need more than one-year follow-up? I just think it's worth raising this discussion, particularly because some of the things that are more theoretical, and presumably rarer, but are the things we worry most about, like autoimmunity, are things that are not likely to be detected in very short-term studies.

The second half of that is, what are the safety endpoints that really need to be collected? Some of the short-term ones are obvious, but some of the more intermediate-term ones, I think, are less obvious, at least to me. It would be helpful to offer some guidance on what those safety endpoints might be.

The final point -- again, to go to something Dr. Jackson brought up and something I mentioned earlier -- I feel very strongly that the appropriate controls for these studies -- that it is appropriate to have randomized saline placebo-controlled controls for these studies, because I think that's the only way you are really going to be able to have any confidence in your safety conclusions. I think having a placebo that has its own toxicities is going to confound the ability to evaluate safety.

There seems to be an ethical rationale for wanting to do that, in the sense of being able to offer some benefit to those who get randomized to the control group. I would be interested to know what others think, but to me that seems like an inaccurate ethical conclusion. There's nothing unethical about randomizing the control group to a saline placebo, and there is no ethical imperative to randomize them to something that offers them some sort of off-target possibility of benefit.

DR. MODLIN: I don't know if others want to address that. I think the obvious reason why the placebo contains adjuvant is to understand what added toxicity

there may be to the vaccine component itself, which is difficult to know if you don't have an adjuvant-containing placebo. I think, under ideal circumstances, you might want to do both, which would give you the maximum information about toxicity.

Norm?

DR. BAYLOR: I want to make a comment about the -- when we compare what we did with the Sanofi vaccine, the landscape was different than it is now. As I hear some of the discussion about size and some of the numbers that have been thrown out, we are in a difficult position. If the pandemic doesn't come tomorrow, theoretically I can collect more data. The longer the pandemic is delayed, the more data I can collect. You have to look at the timeframe when you are thinking about licensure. We do know that as we collect data -- and, say, the pandemic did come tomorrow -- we could use an emergency-use authorization. At least we would have some data to base it on.

But it begs the question of when you stop collecting the data. As these trials are going on and you have an endpoint of licensure, you have to keep that in mind. If the emergency was tomorrow, you may not be able to collect all of the data you want, but you would be able to collect some.

I guess I would like some comment on -- look at this in a timeframe. We still have time to collect

data. Where do we draw that line and say, this is sufficient for licensure or this is sufficient for use in case we have that outbreak coming sooner than later? I think those are different scenarios. I think more time we have, the more time we have to collect additional data.

Some of the numbers that were thrown out, some of the ideas that were thrown out seemed a minimum. Was that because of the urgency? If this happens tomorrow -- or would you say, even if it didn't, you would feel that was sufficient? What you threw out, Pam, would you feel that was sufficient, regardless?

DR. MCINNES: I'm still in the hundreds. I'm thinking about not just one vaccine. It could be a whole series of vaccines that you are collecting a body of data on. I think you might titrate your decision, depending on what you were seeing across the spectrum of vaccines.

If I could ask for a clarification, Norm: Are you really envisioning non-deployment until -- you want data for non-deployment of vaccine, and deployment only in the face of pandemic? Or are we talking about a scenario where you might be trying to prime a population in pre-pandemic?

DR. BAYLOR: We really wanted to stay away from the pre-pandemic. I think the pre-pandemic gets a bit more complicated.

DR. MCINNES: Right. So we are talking about a body of data for deployment in the event of a pandemic.

DR. BAYLOR: Yes.

DR. MODLIN: Once you have safety data with a manufacturer's vaccine that is made according to a certain process, that contains a stable adjuvant that you know a fair amount about, you have an adequate safety database, perhaps, with a few hundred people, particularly if you apply Seth's math to the risk/benefit ratio -- being able to tolerate a relatively low number, but definable adverse outcomes, in the face of a pandemic.

As time goes on, the influenza antigen is going to change. Inevitably, the manufacturer is going to want to come back and update at least the antigen in the vaccine, to the point where I think most of the information that you are going to need is going to be on immunogenicity at that point, and probably the safety issues are going to become slightly less important with an individual vaccine that is made according to the same standard. Is that not the case?

DR. BAYLOR: I'm not so sure.

DR. MODLIN: It's basically getting at the question that was raised earlier: How small a database can you use, given the fact that we are looking at pandemic vaccines?

José?

DR. ROMERO: Norm said something that triggered a thought. What is the sense of urgency that we have for this? These cases have occurred outside of the continent of the Americas. Would our sense of urgency change if, for

example, in Latin America, in Mexico, where -- somebody said running around with chickens. I remember running around with chickens in my grandfather's and grandmother's batio (phonetic). Would this prompt us to change our view of this? Norm's comment about the sense of urgency -- would our approach to this change if this year they report a case of human disease in Latin America?

DR. MODLIN: I think the answer is, without a doubt it would change.

Seth?

DR. HETHERINGTON: I just want to make one comment also to Norm's statement about pre-pandemic versus pandemic. While I think the urgency for a pandemic preparedness is obviously at the forefront, I hope that the FDA and the manufacturers are thinking about a pathway to a pre-pandemic scenario and what would be acceptable for approval. There is very good reason to think there are benefits to priming this population, assuming that you get whatever additional safety data is necessary to feel comfortable about that. Now, that's going to be probably an order of magnitude in terms of safety data than you would be willing to accept for a pandemic vaccine. But the benefits are probably also an order of magnitude greater to have a primed population.

So I just hope that that's being discussed and considered. I'm sure the manufacturers are moving toward that direction in their own thinking.

DR. BAYLOR: It definitely is. In fact, we did present some scenarios of that a couple of VRBPACs ago. So that is ongoing.

DR. STAPLETON: Along the same line, and echoing what Pamela was, I think, implying, perhaps the numbers that you need are not that much beyond what we have, but in going forward, looking at whether clade 1 primes well for different clade 2s, what kinds of immune responses you get to clade 2, whether clade 2 is better at priming -- those types of kinetics experiments would be probably more helpful.

DR. MODLIN: Further comments? Norm?

DR. BAYLOR: I'm going to back up a little bit. I want to go back to the second part of question 1, if I may, on the adult data -- we touched on that lightly -- the adult data needed prior to going into those pediatric studies. As you have been presented today, there are adult studies ongoing. Are those sufficient to move into the pediatric population? Say, for instance, we had an adjuvant that was not discussed today or a novel manufacturing process that was not discussed today. From what you have seen today, are those the types of numbers in the adults that would be adequate to move into the pediatric population?

DR. MODLIN: The numbers we saw were tens of thousands of adults that were being tested, so I would

think, certainly, that the answer would be yes, from my standpoint.

Does anybody feel any differently?

Are you asking us how many adults would need to be tested to be confident to go into the pediatric population?

DR. BAYLOR: Yes.

DR. MCINNES: I would want to see more numbers in adults than for children. I think you want to be very confident that you have characterized the safety and immunogenicity profile in adults.

DR. MODLIN: Can I push you a little bit, Pam? Is that for -- adequate to assess adverse events that we would consider to be relatively uncommon or adequate to assess adverse events like Guillain-Barré syndrome that are extraordinarily rare, the 1 per 100,000, the 1 per 1 million?

DR. MCINNES: No. I'm talking about characterizing events that are more temporally related to vaccination.

DR. MODLIN: Norm, it's 2:55. Is there anything that we haven't addressed, either for you or Dr. Nelson or Dr. Pratt?

DR. BAYLOR: I guess not.

DR. MODLIN: I do know people have cabs waiting and need to get off to the airport. I do want to express my personal thanks to all the members of the committee,

those that have joined us as voting members. Certainly terrific presentations from the FDA and from industry. Thank you, everyone. See you at the next meeting.

(Whereupon, at 3:00 p.m., the meeting was adjourned.)